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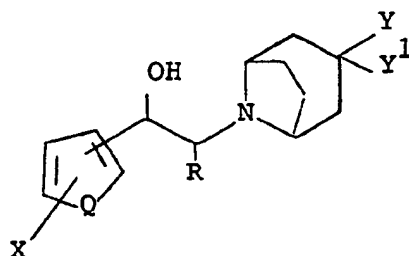
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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US89/02176 <b>(22) International Filing Date:</b> 17 May 1989 (17.05.89) <b>(71) Applicant (for all designated States except US):</b> PFIZER, INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US). <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> CHENARD, Bertrand, L. [US/US]; 7 Whaling Drive, Waterford, New London County, CT 06385 (US). <b>(74) Agents:</b> RICHARDSON, Peter, C. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).		<b>(81) Designated States:</b> FI, HU, NO, RO, SU, US.  <b>Published</b> <i>With international search report.</i>

**(54) Title:** 2-PIPERIDINO-1-ALKANOL DERIVATIVES AS ANTIISCHEMIC AGENTS

(I)

**(57) Abstract**

2-(8-Azabicyclo[3.2.1]oct-8-yl)alkanols of formula (I), wherein Q is S or CH=CH; X is H, OH or another aromatic substituent; R is hydrogen, alkyl, alkenyl or alkynyl; Y and Y<sup>1</sup> are taken together and are arylmethylene or aralkylmethylene (or a corresponding epoxy derivative) or Y and Y<sup>1</sup> are taken separately and Y is hydrogen or OH, and Y<sup>1</sup> is aryl, aralkyl, arylthio, or aryloxy; and structurally related 2-(piperidino)alkanols; pharmaceutical compositions thereof; methods of treating CNS disorders therewith; and intermediates useful in the preparation of said compounds.

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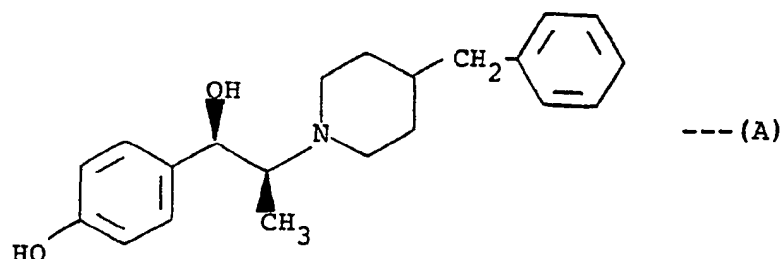
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2-PIPERIDINO-1-ALKANOL DERIVATIVES  
AS ANTIISCHEMIC AGENTS

Background of the Invention

The present invention is directed to neuroprotective (antiischemic and excitory aminoacid receptor blocking) 2-piperidino-1-alkanol derivatives defined by the formulas (I), (II) and (III) below; pharmaceutically acceptable salts thereof; a method of using these compounds in the treatment of stroke or CNS degenerative diseases such as Alzheimer's disease, Huntington's disease and Parkinson's disease; and to certain intermediates therefor.

Ifenprodil is a racemic, so-called dl-erythro compound having the relative stereochemical formula



which is marketed as a hypotensive agent, a utility shared by a number of close analogs; Carron et al., U.S. Patent 3,509,164; Carron et al., Drug Res., v. 21, pp. 1992-1999 (1971). More recently, ifenprodil has been shown to possess antiischemic and excitory aminoacid receptor blocking activity; Gotti et al., J. Pharm. Exp. Therap., v. 247, pp. 1211-21 (1988); Carter et al., loc. cit., pp. 1222-32 (1988).

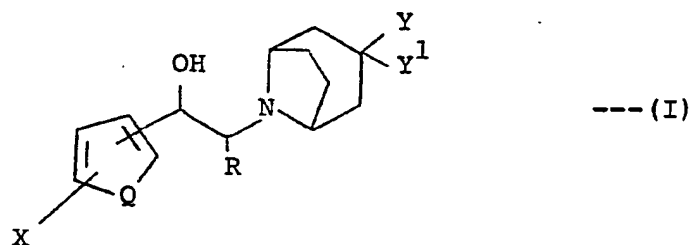
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See also French Patent 2546166. A goal, substantially met by the present invention, has been to find compounds possessing such neuroprotective effect in good measure, while at the same time having lowered or no significant hypotensive effect.

Certain structurally related 1-phenyl-3-(4-aryl-4-acyloxypiperidino)-1-propanols have also been reported to be useful as analgesics, U.S. Patent 3,294,804; and 1-[4-(amino- and hydroxy-alkyl)phenyl]-2-(4-hydroxy-4-tolylpiperazino)-1-alkanols and alkanones have been reported to possess analgesic, antihypertensive, psychotropic or antiinflammatory activity, Japanese Kokai 53-02,474 (CA 89:43498y; Derwent Abs. 14858A) and 53-59,675 (CA 89:146938w; Derwent Abs. 48671A).

#### Summary of the Invention

The present invention is directed to compounds of the formula



wherein

R is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl or (C<sub>2</sub>-C<sub>6</sub>)alkynyl;

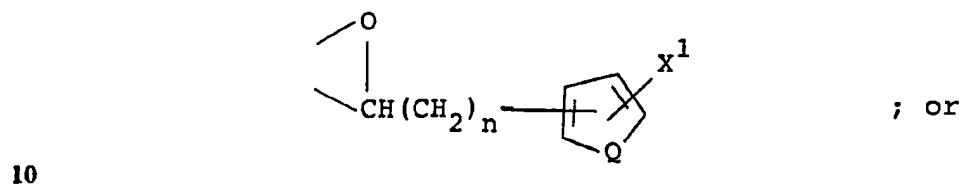
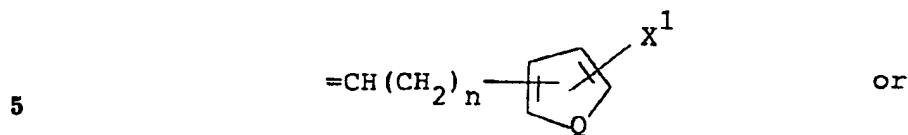
X is hydrogen, (C<sub>1</sub>-C<sub>3</sub>)alkyl, halo, OR<sup>1</sup>, OCOR<sup>1</sup>, SR<sup>1</sup>, NHR<sup>1</sup>, NHCOR<sup>1</sup>, CONH<sub>2</sub> or CN;

R<sup>1</sup> is hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl;

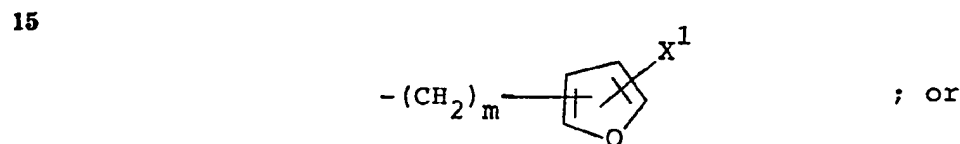
Q is S or CH=CH;

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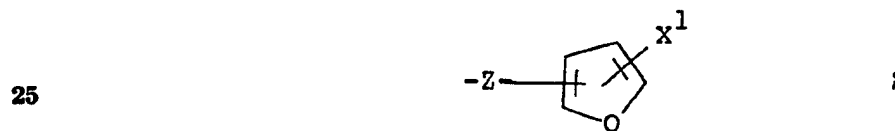
$Y$  and  $Y^1$  are taken together and are



Y and Y<sup>1</sup> are taken separately, and  
Y is hydrogen or OH, and Y<sup>1</sup> is



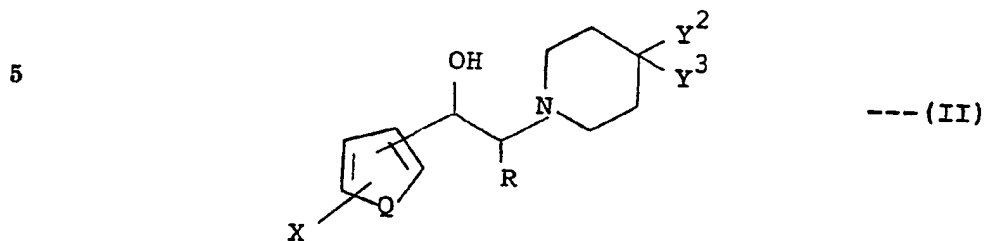
20                    y is hydrogen and  $y^1$  is



30           n is 0, 1, 2 or 3;  
          m is 0, 1, 2, 3 or 4;  
          Q<sup>1</sup> is independently a value of Q as defined above;  
          X<sup>1</sup> is independently a value of X as defined above;  
          and  
          Z is O, S, SO or SO<sub>2</sub>;

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compounds of the formula

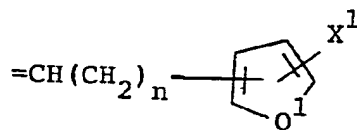


10

wherein

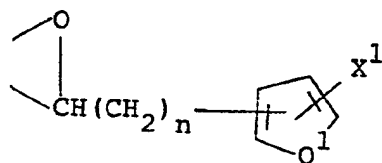
$Y^2$  and  $Y^3$  are taken together and are

15



or

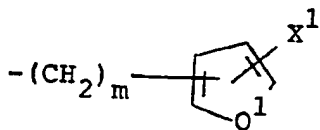
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; or

25

$Y^2$  and  $Y^3$  are taken separately, and  $Y^2$  is OH and  $Y^3$  is



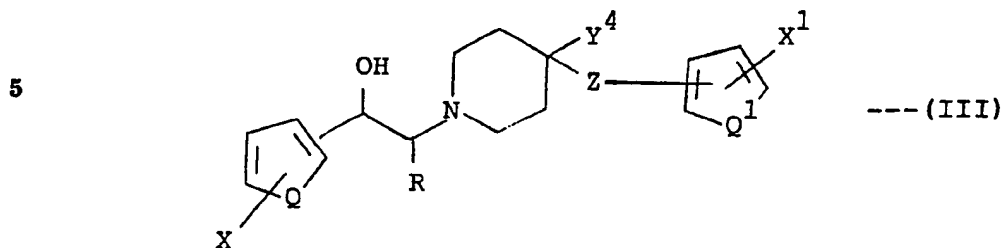
;

30

and R,  $R^1$ , X,  $X^1$ , Q,  $Q^1$ , n and m are as defined above;

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and compounds of the formula



10

wherein

$Y^4$  is H; and

R,  $R^1$ , Q,  $Q^1$ , X,  $X^1$  and Z are as defined above;

and the pharmaceutically acceptable acid addition salts  
15 of these compounds.

15

The expression "pharmaceutically acceptable acid  
addition salts" is intended to include but is not  
limited to such salts as the hydrochloride, hydro-  
bromide, hydroiodide, nitrate, hydrogen sulfate,  
20 dihydrogen phosphate, mesylate, maleate, and succinate.  
Such salts are conventionally prepared by reacting the  
free base form of the compound (I), (II) or (III) with  
an appropriate acid, usually one molar equivalent, and  
in a solvent. Those salts which do not precipitate  
25 directly are generally isolated by concentration of the  
solvent and/or addition of a non-solvent.

25

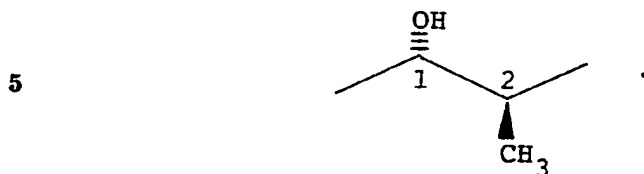
The preferred compounds of the present invention  
generally have R as methyl and possess 1S\*, 2S\* or threo  
relative stereochemistry at the 1- and 2-positions of  
30

30



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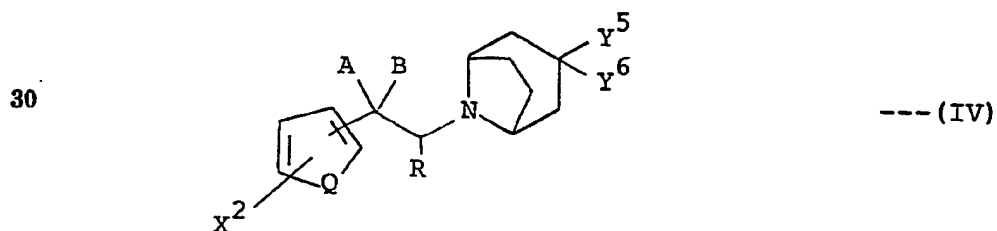
the propanol chain, i.e.,



10 Furthermore, regardless of the value of R, preferred compounds of the present invention are of the formula (I) or (II) having Y and Y<sup>1</sup> or Y<sup>2</sup> and Y<sup>3</sup> taken separately, further having Y or Y<sup>2</sup> as OH, or Y<sup>1</sup> as -Z(C<sub>4</sub>H<sub>3</sub>O<sup>1</sup>)X<sup>1</sup>; or are of the formula (III). The preferred value of Z in all cases is S.

15 The present invention is also directed to pharmaceutical compositions and to methods of treating a mammal, particularly man, suffering a central nervous disorder, which comprises administering to said mammal a neuroprotective effective amount of a compound of the  
20 formula (I), (II) or (III). Said compositions and methods are particularly valuable in the treatment of stroke, Alzheimer's disease, Parkinson's disease, Huntington's disease and related disorders of the central nervous system.

25 The present invention is further directed to intermediate compounds of the formula



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wherein

A and B are taken together and are oxygen,  
forming, together with the carbon to which they are  
attached a carbonyl group, or A and B are taken  
separately and A is hydrogen and B is hydroxy;

$X^2$  is hydrogen,  $(C_1-C_3)$ alkyl, halo,  $OR^1$ ,  $OR^2$ ,  
 $OCOR^1$ ,  $SR^1$ ,  $SR^2$ ,  $NHR^1$ ,  $NR^1R^3$ ,  $NHCOR^1$ ,  $CONH_2$  or CN;

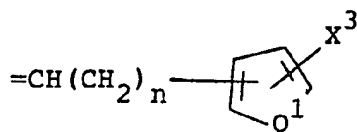
$R^1$  is hydrogen or  $(C_1-C_3)$ alkyl;

$R^2$  is a conventional hydroxy or mercaptan  
protecting group;

$R^3$  is a conventional amino protecting group;

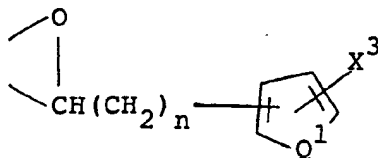
$Y^5$  and  $Y^6$  are taken together and are

15



or

20



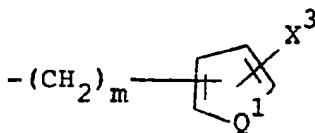
; or

25

$Y^5$  and  $Y^6$  are taken separately and

$Y^5$  is hydrogen or OH, and  $Y^6$  is

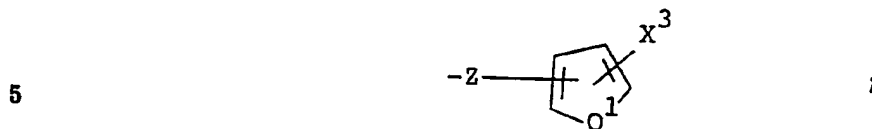
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; or

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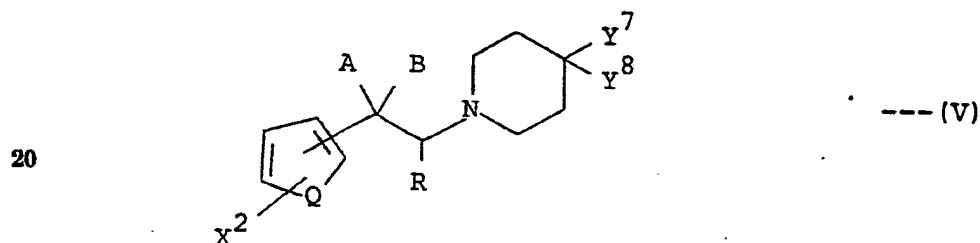
$Y^5$  is hydrogen and  $Y^6$  is



10  $X^3$  is independently a value of  $X^2$  as defined above; with the proviso that when A and B are taken separately, at least one of  $X^2$  and  $X^3$  is  $OR^2$ ,  $SR^2$  or  $NR^1R^3$ ;

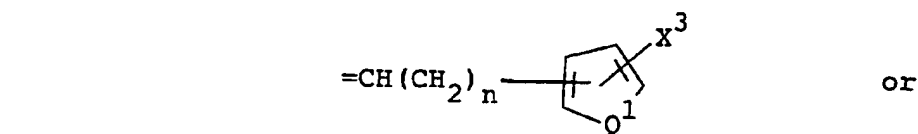
Z is O, S, SO or  $SO_2$ ; and

15 R, Q,  $Q^1$ , n and m are as defined above; intermediate compounds of the formula

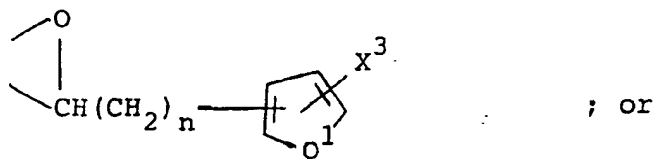


wherein

25  $Y^7$  and  $Y^8$  are taken together and are



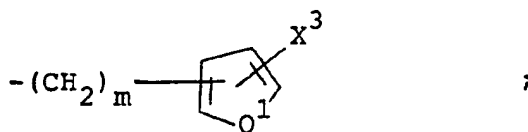
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5

$Y^7$  and  $Y^8$  are taken separately, and  $Y^7$  is OH and  $Y^8$  is

10

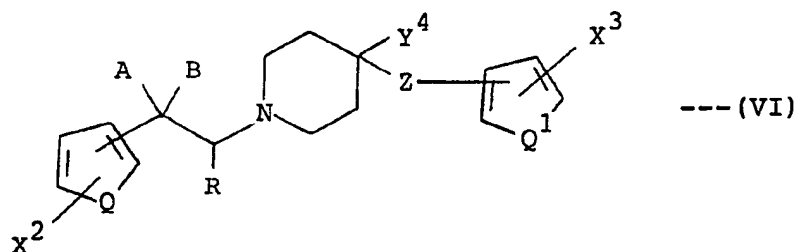


15

and A, B, R,  $R^1$ ,  $R^2$ ,  $R^3$ , Q,  $Q^1$ ,  $X^2$ ,  $X^3$ , n and m are as defined above, with the same proviso concerning A and B;

and intermediate compounds of the formula

20



25

wherein all groups are defined as above, with the same proviso concerning A and B.

30

Those compounds of the formula (I) or (IV) specified as endo have the hydroxy group or oxirane oxygen on the same side of the piperidine ring as the ethylene bridge.

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It will be noted that those compounds of the formula (I) to (VI) which are 1-alkanols possess an asymmetric C-1 carbon, while those wherein R is other than hydrogen possess a second asymmetric center at the C-2 carbon of the alcohol. Similarly, in those compounds of the formulas (IV) to (VI) which are 1-alkanones wherein R is other than hydrogen possess a C-2 asymmetric carbon. It will be evident to those skilled in the art of organic chemistry, therefore, that such compounds can be resolved into optical isomers showing equal but opposite rotation of plane polarized light. For example, all of these compounds are potentially resolved by fractional crystallization of their diastereomeric addition salts with an optically active acid; while the alcohols are also potentially resolved by chromatography or fractional crystallization of esters derived by reaction with activated forms of optically active acids or with optically active isocyanates. Thus, the present invention should not be construed as limited to the racemic forms of the present compounds.

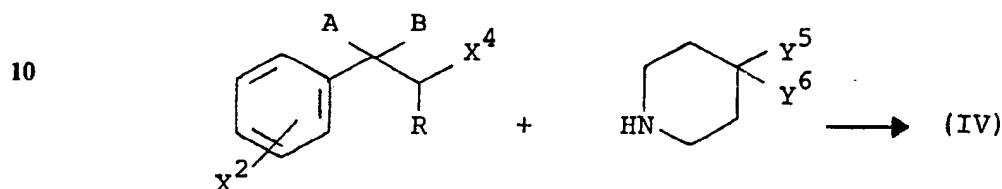
#### Detailed Description of the Invention

The compounds of the present invention, having the formula (I), (II) and (III) defined above, are readily and generally prepared by nucleophilic displacement followed by reduction of the resulting ketone to alcohol as detailed below.

The precursor ketones are generally initially prepared with -OH, -SH and -NHR<sup>1</sup> groups in protected form, i.e., as -OR<sup>2</sup>, -SR<sup>2</sup> or -NR<sup>1</sup>R<sup>3</sup> groups in the compounds of the formulas (IV), (V) and (VI) where A and B are taken together as oxygen to form a carbonyl

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group. Such protected ketones are generally formed by nucleophilic displacement of an appropriately substituted 2-halo, 2-alkanesulfonyloxy- or 2-arylsulfonyloxy-1-alkanone with an appropriately substituted piperidine derivative, e.g.,



15 wherein  $X^4$  is typically chloro, bromo, mesyloxy or tosyloxy. This reaction is carried out under conditions typical of nucleophilic displacements in general. Where the two reactants are about equivalent in availability, close to substantially molar equivalents may be used; although when one is more readily available, it is usually preferred to use that one in excess, in order to force this bimolecular reaction to completion in a shorter period of time. The reaction is generally carried out in the presence of at least 1 molar equivalent of a base, the piperidine derivative itself, if it is readily available, but more usually a tertiary amine which is at least comparable in base strength to the nucleophilic piperidine; and in a reaction inert solvent such as ethanol. If desired, the reaction is catalyzed by the addition of up to one molar equivalent or more of an iodide salt (e.g., NaI, KI). Temperature

20

25

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is not critical, but will generally be somewhat elevated in order to force the reaction to completion within a shorter time period, but not so high as to lead to undue decomposition. A temperature in the  
5 range of 50-120°C is generally satisfactory. Conveniently, the temperature is the reflux temperature of the reaction mixture.

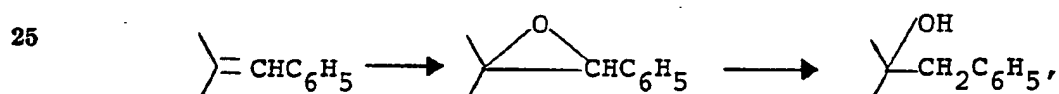
As used in the preceding paragraph, and elsewhere  
10 herein, the expression "reaction inert solvent" refers to any solvent which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

15 If desired, those ketone intermediates having OH, SH or  $\text{NHR}^1$  groups in protected form ( $\text{OR}^2$ ,  $\text{SR}^2$  or  $\text{NR}^1\text{R}^3$ ) can be deprotected at this stage by conventional methods. For example, when  $\text{R}^2$  is triisopropylsilyl or tert-butyldimethylsilyl, the protecting group is  
20 conveniently removed by reaction with tetrabutylammonium fluoride (generally, substantially 2 molar equivalents) in a reaction inert solvent such as tetrahydrofuran. When  $\text{R}^2$  is benzyl or  $\text{R}^3$  is benzyloxycarbonyl, the protecting group will generally  
25 be removed by conventional hydrogenolysis over a noble metal catalyst in a reaction inert solvent, e.g., using 10% Pd/C as catalyst, preferably at low pressures (e.g., 1-10 atmospheres) and temperatures (e.g., 20-75°C) and generally in a reaction inert solvent such  
30 as methanol.

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Generally excluding ketone intermediates containing ester groups or protecting groups such as benzyloxycarbonyl (which will generally be removed prior to ketone reduction), but otherwise with or without prior removal of protecting groups, the ketone intermediates are conveniently converted to corresponding alcohols by conventional reduction with a  $\text{LiAlH}_4$ , usually in excess (e.g., mol for mol), in a reaction inert solvent such as tetrahydrofuran at reduced temperature (e.g.,  $-15^\circ\text{C}$  to  $15^\circ\text{C}$ ). Alternatively, ketone intermediates, particularly those containing ester groups, are reduced with a milder hydride reducing agent such as  $\text{NaBH}_4$ , again usually in excess, now in a protic solvent such as methanol or ethanol, generally at somewhat higher temperature, e.g.,  $15-45^\circ\text{C}$ .

Any protecting groups which are still in place after ketone reduction are then removed according to the methods described above. Certain other transformations, such as olefin hydrogenation, epoxidation and sodium/liquid  $\text{NH}_3$  reduction of epoxides, e.g.,



are also optionally carried out late in the synthetic sequence, e.g., after coupling to form ketone, after removal of protecting groups (so long as the unprotected groups do not interfere with the transformations) and/or after reduction of ketone to alcohol.

Said epoxidations are readily accomplished, for example, by reacting a methylene compound with



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substantially one molar equivalent of m-chloro-perbenzoic acid in a reaction inert solvent such as  $\text{CH}_2\text{Cl}_2$ . The reduction of epoxide to alcohol is readily accomplished by conventional sodium/liquid ammonia, generally carried out at temperatures below the boiling point of liquid  $\text{NH}_3$  (e.g., at  $-78^\circ\text{C}$ , the temperature of an acetone-dry ice bath) in the presence of a reaction inert solvent such as tetrahydrofuran.

The starting materials and reagents required for the synthesis of the compounds of the present invention are readily available, either commercially, according to literature methods, or by methods exemplified in Preparations below.

The present compounds of the formula (I), (II) and (III) possess selective neuroprotective activity, based upon their antiischemic activity and ability to block excitatory amino acid receptors, while at the same time having lowered or no significant hypotensive activity.

The antiischemic activity of the present compounds is determined according to one or more of the methods which have been detailed previously by Gotti *et al.* and Carter *et al.* cited above, or by similar methods. The ability of the compounds of the present invention to block excitatory amino acid receptors is demonstrated by their ability to block N-methyl-D-aspartic acid-induced (NMDA) elevations of cGMP in neonatal rat cerebellums according to the following procedure. Cerebellums from ten 8-14 day old Wistar rats are quickly excised and placed in  $4^\circ\text{C}$ . Krebs/bicarbonate buffer, pH 7.4 and then chopped in 0.5 mm x 0.5 mm sections using a McIlvain tissue chopper (The Nickle Laboratory Engineering Co., Gomshall, Surrey, England). The resulting pieces of cerebellum are transferred to 100 ml of

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Krebs/bicarbonate buffer at 37° C. which is continuously equilibrated with 95:5 O<sub>2</sub>/CO<sub>2</sub>. The pieces of cerebellum are incubated in such a manner for ninety minutes with three changes of the buffer. The buffer then is  
5 decanted, the tissue centrifuged (1 min., 3200 r.p.m.) and the tissue resuspended in 20 ml of the Krebs/bicarbonate buffer. Then, 250 µl aliquots (approximately 2 mg) are removed and placed in 1.5 ml microfuge tubes. To those tubes are added 10 µl of the compound under  
10 study from a stock solution followed, after a 10 minute incubation period, by 10 µl of a 2.5 mM solution of NMDA to start the reaction. The final NMDA concentration is 100 µM. Controls do not have NMDA  
15 added. The tubes are incubated for one minute at 37° C. in a shaking water bath and then 750 µl of a 50 mM Tris-Cl, 5mM EDTA solution is added to stop the reaction. The tubes are placed immediately in a boiling  
20 water bath for five minutes. The contents of each tube then are sonicated for 15 seconds using a probe sonicator set at power level three. Ten microliters are removed and the protein determined by the method of Lowry, Anal. Biochem. 100:201-220 (1979). The tubes are then  
25 centrifuged (5 min., 10,000 xg), 100 µl of the supernatant is removed and the level of cyclic GMP (cGMP) is assayed using a New England Nuclear (Boston, Massachusetts) cGMP RIA assay according to the method of the supplier. The data is reported as pmole cGMP generated per mg. protein. Undesired hypotensive  
30 activity is also determined by known methods, for example, according to the methods of Carron et al., also cited above.

Such selective neuroprotective antiischemic and excitatory amino acid blocking activities reflect the

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valuable utility of the present compounds in the treatment of degenerative CNS (central nervous system) disorders such as stroke; and Alzheimer's disease, Parkinson's disease and Huntington's disease; without significant potential for concurrent undue drop in blood pressure. In the systemic treatment of such diseases with a neuroprotective amount of compounds of the formula (I), (II) or (III), the dosage is typically from about 0.02 to 10 mg/kg/day (1-500 mg/day in a typical human weighing 50 kg) in single or divided doses, regardless of the route of administration. Of course, depending upon the exact compound and the exact nature of the individual illness, doses outside this range may be prescribed by the attending physician. The oral route of administration is generally preferred. However, if the patient is unable to swallow, or oral absorption is otherwise impaired, the preferred route of administration will be parenteral (i.m., i.v.) or topical.

The compounds of the present invention are generally administered in the form of pharmaceutical compositions comprising at least one of the compounds of the formula (I), (II) or (III), together with a pharmaceutically acceptable vehicle or diluent. Such compositions are generally formulated in a conventional manner utilizing solid or liquid vehicles or diluents as appropriate to the mode of desired administration: for oral administration, in the form of tablets, hard or soft gelatin capsules, suspensions, granules, powders and the like; for parenteral administration, in the form of injectable solutions or suspensions, and

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the like; and for topical administration, in the form of solutions, lotions, ointments, salves and the like.

The present invention is illustrated by the following examples, but is not limited to the details thereof.

All non-aqueous reactions were run under nitrogen for convenience and generally to maximize yields. All solvents/diluents were dried according to standard published procedures or purchased in a predried form. All reactions were stirred either magnetically or mechanically. NMR spectra are recorded at 300 MHz and are reported in ppm. The NMR solvent was  $\text{CDCl}_3$  unless otherwise specified. IR spectra are reported in  $\text{cm}^{-1}$ , generally specifying only strong signals.

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EXAMPLE 1

2-(3-Phenylmethylen-8-azabicyclo[3.2.1]oct-8-yl)-1-  
(4-(triisopropylsilyloxy)phenyl)-1-propanone

5 A mixture of 3-phenylmethylen-8-azabicyclo-  
[3.2.1]octane (1.09 g, 4.87 mmol), 4-(triisopropyl-  
siloxy)-alpha-bromopropiophenone (1.88 g, 4.88 mmol)  
and triethylamine (1.5 ml, 10.76 mmol) in ethanol (75  
ml) was refluxed 22 hours. After cooling, ether (50  
10 ml) was added and the mixture was filtered through  
diatomaceous earth. The filtrate was concentrated and  
chromatographed on silica gel (2 x 6 inches, hexane  
then ethyl acetate/hexane gradient) to give 0.56 g  
(23%) of an orange oil product; NMR 8.18 (d, 2H), 7.25  
15 (t, 2H), 7.12 (d, 3H), 6.86 (d, 2H), 6.29 (s, 1H), 4.08  
(m, 1H), 3.47-3.26 (m, 2H), 2.75 (m, 1H), 2.57-2.37 (m,  
2H), 2.03-1.72 (m, 4H), 1.6 (m, 1H; partially under  
water peak from NMR solvent), 1.40 (d, 3H), 1.25 (m,  
3H), 1.09 (d, 18H).

20

EXAMPLE 2

Mixture of (1R\*,2S\*)- and (1S\*,2S\*)-2-(3-  
phenylmethylen-8-azabicyclo[3.2.1]oct-8-yl)-  
1-(4-(triisopropylsilyloxy)phenyl)-1-propanol

To a slurry of  $\text{LiAlH}_4$  (0.61 g, 16.07 mmol) in  
25 tetrahydrofuran (50 ml) at 0°C was added title product  
of the preceding Example (8.04 g, 15.96 mmol) in  
tetrahydrofuran (150 ml) over 15 minutes. The mixture  
was stirred 15.5 hours at room temperature, then  
carefully quenched with water (1.2 ml), filtered over  
30 diatomaceous earth and concentrated to give a yellow  
oil (7.15 g, 89%). This mixture of racemic title  
products was used directly in the next reaction without  
purification.

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EXAMPLE 3

(1S\*,2S\*)- and (1R\*,2S\*)-1-(4-hydroxyphenyl)-2-(3-phenylmethylene-8-azabicyclo[3.2.1]oct-8-yl)-1-propanol

5 Title product of the preceding Example (7.15 g, 14.14 mmol) was dissolved in tetrahydrofuran (250 ml) and tetrabutylammonium fluoride (28.5 ml, 28.5 mmol, 1M in tetrahydrofuran) was added all at once. The solution was stirred at room temperature 18 hours, then  
10 concentrated and chromatographed on silica gel (4 x 6 inches, ethyl acetate/hexane gradient followed by methanol/ethyl acetate gradient) to give first the racemic (1S\*,2S\*)-title product (1.58 g) followed by the more polar racemic (1R\*,2S\*)-title product (2.88  
15 g). (Note that because of the asymmetry in the 3-phenylmethylene-8-azabicyclo[3.2.1]oct-8-yl side chain, each of these products is actually a mixture of two racemates).

20 The (1S\*,2S\*)-product was recrystallized from ethyl acetate/hexane to give 0.923 g of white solid; mp 175-177°C; NMR includes 4.10 (t, J=7.7Hz, 1H); Anal. C 78.77, H 7.90, N 3.92, calcd. C 79.05, H 7.90, N 3.92.

25 The (1R\*,2S\*)-product was further purified by radial chromatography with 60% ethyl acetate/hexane elution to give 0.24 g of colorless oil. This oil was crystallized from ether/hexane to give 0.17 g of fluffy solid, mp 78.5-85°C. The latter was converted to its HCl salt by bubbling HCl gas into an ether solution of  
30 the compound for 3 minutes. The white precipitate was collected and recrystallized from ethanol to yield the (1R\*,2S\*)-hydrochloride salt as its half hydrate; mp 215-218°C; NMR (DMSO-d<sub>6</sub>) includes 5.17 (s, 1H) and 4.60-3.93 (m, 2H); Anal. C 70.00, H 7.45, N 3.35, calcd. for  $\frac{1}{2}$  H<sub>2</sub>O C 69.95, H 7.40, N 3.54.

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EXAMPLE 42-(4-(Phenylthio)piperidino)-1-(4-(tert-butyldimethylsilyloxy)phenyl)-1-propanone

5 This product was prepared according to the procedure of Example 1 using 4-phenylthiopiperidine (1.13 g, 5.85 mmol), triethylamine (0.82 ml, 5.88 mmol), and 4-(tert-butyldimethylsilyloxy)-alpha-bromopropiophenone (2.0 g, 5.83 mmol) and a reflux time of 10 21.5 hours. The product was isolated by silica gel flash chromatography with an ethyl acetate/hexane gradient elution. The yield was 1.29 g of title product as a yellow oil: NMR 8.00 (d, J = 9Hz, 2H), 7.35 (d, J = 7.8Hz, 2H), 7.25 (m, 3H), 6.81 (d, J = 8.4Hz, 2H), 4.00 (q, J = 6.8Hz, 1H), 3.03 (m, 1H), 15 2.91-2.87 (m, 1H), 2.80-2.76 (m, 1H), 2.44 (dt, J = 9.5, 2.6Hz, 1H), 2.29-2.19 (m, 1H), 1.93-1.85 (m, 2H), 1.66-1.52 (m, 2H--partially under water peak from solvent), 1.22 (d, J = 7.1Hz, 3H), 0.97 (s, 9H), 0.22 20 (s, 6H). Later fractions from the chromatography yielded an additional 0.51 g of product which had desilylated during the reaction. This material could also be converted to the final targeted compounds by procedures below.

25 By the same methods 4-(triisopropylsilyloxy)-alpha-bromopropiophenone (9.97 g, 25.9 mmol) was converted to chromatographed 2-(4-(phenylthio)piperidino)-1-(4-(triisopropylsilyloxy)phenyl)-1-propanone as a light orange oil: 8.32 g; NMR 8.00 (d, J = 8.8Hz, 2H), 7.37 (dd, J = 1.5, 8.4Hz, 2H), 7.29-7.18 (m, 3H), 6.86 (d, J = 8.8Hz, 2H), 4.02 (q, J = 6.8Hz, 1H), 3.08-3.00 (m, 1H), 2.85 (d, J = 26.2Hz, 1H), 2.75 (d, J = 16.6Hz, 1H), 2.45 (dt, J = 11, 2.6Hz, 1H), 2.23 (dt, J = 9.8, 2.5Hz, 1H), 1.96-1.88 (m, 2H), 1.71-1.50 (m, 5H), 1.09 (d, J = 7Hz, 18H).

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EXAMPLE 5

(1S\*,2S\*)- and (1R\*,2S\*)-2-(4-Phenylthio)piperdino)-  
1(4-(triisopropylsilyloxy)phenyl)-1-propanol

5 By the method of Example 2, the triisopropyl-  
silyloxy product of the preceding Example (8.32 g, 16.7  
mmol), using chromatography on silica gel with ethyl  
acetate/hexane gradient elution to separate the  
isomers, was converted to 6.06 g of less polar (1S\*,  
10 2S\*)-title product as an oil; NMR 7.41 (d, J = 6.7Hz,  
2H), 7.32-7.24 (m, 3H), 7.15 (d, J = 8.5Hz, 2H), 6.82  
(d, J = 8.4Hz, 2H), 4.14 (d, J = 9.7Hz, 1H), 3.11 (m,  
1H), 2.88 (m, 1H), 2.69 (m, 1H), 2.69-2.55 (m, 2H),  
2.21 (t, 1H), 2.03 (m, 2H), 1.85-1.58 (m, 3H),  
15 1.35-1.20 (m, 2H), 1.23 (d, J = 15Hz, 18H), 1.07 (d, J  
= 7Hz, 3H); and to 0.2 g of more polar (1R\*,2S\*)-title  
product; NMR 7.35 (d, J = 7Hz, 2H), 7.28-7.16 (m, 3H),  
7.08 (d, J = 9Hz, 2H), 6.78 (d, J = 9Hz, 2H), 4.68 (d,  
J = 5Hz, 1H), 3.10-2.98 (m, 1H), 2.98-2.87 (m, 1H),  
20 2.75-2.60 (m, m, 2H), 2.33 (t, J = 9Hz, 1H), 2.16 (t, J  
= 11Hz, 1H), 1.91 (t, J = 15Hz, 2H), 1.70-1.48 (m, 2H),  
1.32-1.12 (m, 4H), 1.06 (d, J = 9Hz, 18H), 0.88-0.78  
(m, 3H).

EXAMPLE 6

25 (1S\*,2S\*)-1-(4-Hydroxyphenyl)-2-(4-(phenylthio)-  
piperidino)-1-propanol

Method A

To a slurry of LiAlH<sub>4</sub> (0.11 g, 2.9 mmol) in tetra-  
hydrofuran (25 ml) chilled to 0°C was added title  
30 product of Example 4 (1.29 g, 2.83 mmol) in tetrahydro-  
furan (50 ml). The reaction was warmed to ambient  
temperature for 2 hours, refluxed for 3 hours, and left



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to stir for 72 hours. The mixture was carefully quenched with water and filtered through diatomaceous earth. The filtrate was concentrated to a wet solid, which was taken up in ethyl acetate and washed with brine, dried ( $\text{CaSO}_4$ ), concentrated to afford 0.41 g of white solid, and recrystallized from ether/hexane to give 0.16 g of title product; mp 155-157°C; NMR includes 4.12 (d, 1H); Anal. C 69.57, H 7.28, N 3.95, calcd. C 69.94, H 7.34, N 4.08. The alumina salts from the reaction were Soxhlet extracted with ethyl acetate for 24 hours. Concentration gave an additional 0.3 g of product.

#### Method B

The same product is obtained from the (1S\*, 2S\*)-title product of the preceding Example by the method of Example 3.

#### EXAMPLE 7

(1R\*, 2S\*)-1-(4-Hydroxyphenyl)-2-(4-(phenylthio)-piperidino)-1-propanol

Following the procedure of Example 3, present title product was obtained from the (1R\*, 2S\*)-title of Example 5 (0.2 g, 0.4 mmol) and tetrabutylammonium fluoride (0.8 ml, 0.8 mmol: 1M in tetrahydrofuran) in tetrahydrofuran (5 ml) at ambient temperature for 72 hours. The product was obtained by silica gel flash chromatography (6 x 1 inches, ethyl acetate/hexane gradient elution) to give 0.14 g of semi-solid. Recrystallization from methylene chloride/hexane gave 0.056 g of white solid; mp 124.5-126°C; NMR includes 4.72 (d, J = 4.1Hz, 1H); Anal. C 69.68, H 7.24, N 4.14, calcd. C 69.94, H 7.34, N 4.08.

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EXAMPLE 8

(1S\*,2S\*)-1-(4-Hydroxyphenyl)-2-(4-(phenylsulfonyl)-  
piperidino)-1-propanol

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5 Title product of Example 6 (0.13 g, 0.378 mmol)  
was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and m-chloroperoxy-  
benzoic acid (0.23 g, 1.133 mmol) was added all at  
once. The solution was stirred 23 hours, then the  
precipitated material was filtered to give 0.154 g of  
10 white solid which was the crude intermediate N-oxide.  
The latter was hydrogenated in a Parr apparatus in  
methanol (20 ml) with 10% palladium on carbon catalyst  
(0.03 g) at 50 psig hydrogen. The reaction was  
complete in 6 hours and was filtered through  
15 diatomaceous and concentrated to leave 0.166 g of  
yellow oil. This oil was taken up in CH<sub>2</sub>Cl<sub>2</sub> and washed  
with saturated sodium bicarbonate. The organic phase  
was dried (MgSO<sub>4</sub>) and concentrated to give 0.106 g of  
yellow oil, which was crystallized from ethyl  
20 acetate/hexane to yield 0.076 g of white solid; mp  
169-175°C. A portion of the product (0.045-0.050 g)  
was further purified by mixing vigorously with  
saturated sodium bicarbonate and ethyl acetate for 15  
minutes. The phases were separated and the aqueous was  
25 further extracted with ethyl acetate (2x). The  
combined organic phase was dried (CaSO<sub>4</sub>), concentrated  
to give a colorless oil, and crystallized from ethyl  
acetate to give 0.02 g of white powder; mp 195-196°C;  
NMR 7.88 includes 4.15 (d, J = 9.7Hz, 1H); Anal. C  
30 63.77, H 6.61, N 3.61, calcd. C 63.98, H 6.71, N 3.73.

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EXAMPLE 9

(1S\*,2S\*)-1-(4-Hydroxyphenyl)-2-(4-(phenylsulfinyl)-  
piperidino)-1-propanol

5 Title product of Example 6 (0.5 g, 1.46 mmol) was  
dissolved in CH<sub>2</sub>Cl<sub>2</sub> (40 ml) and m-chloroperoxybenzoic  
acid (0.3 g, 1.48 mmol) was added all at once. After  
stirring overnight at ambient temperature, the mixture  
10 was concentrated directly onto silica gel and flash  
chromatographed (6 x 1 inches, ethyl acetate/hexane  
gradient) to give 0.34 g of crude product as a white  
solid which was further purified by partitioning  
between saturated NaHCO<sub>3</sub> and ethyl acetate with  
vigorous stirring for 20 minutes. The phases were  
15 separated and the organic layer was concentrated to  
leave a greasy solid which was crystallized from ethyl  
acetate/hexane to give 0.122 g of white solid; mp  
110°C; NMR includes 4.16 (long range coupled d, J = 9.7  
Hz, 1H); HRMS 360.1635, calcd. 360.1626.

20 EXAMPLE 10

1-(4-(Benzyloxy)phenyl)-2-(4-benzyl-4-  
hydroxypiperidino)-1-propanone

This product was prepared following the procedure  
of Example 1 from 4-hydroxy-4-benzylpiperidine (2.0 g,  
10.46 mmol), triethylamine (1.46 ml, 10.47 mmol), and  
25 4-benzyloxy- $\alpha$ -bromopropiophenone (3.33 g, 10.43  
mmol) in ethanol (50 ml) with a reflux period of 24  
hours. The present racemic product was obtained after  
silica gel flash chromatography with ethyl  
30 acetate/hexane gradient elution. The yield was 2.88 g  
(64%) of a yellow solid; NMR 8.06 (d, 2H), 7.52-7.08  
(m, 10H), 6.97 (d, 2H), 5.11 (s, 2H), 4.00 (q, 1H),  
2.72 (s, 2H), 2.72-2.53 (m, 2H), 2.43 (t, 1H),  
1.85-1.39 (m, 6H), 1.23 (d, 3H). HRMS 412.2348, calcd.  
(-OH) 412.2273.

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EXAMPLE 11

(1S\*,2S\*)-1-(4-(Benzyloxy)phenyl)-2-(4-benzyl-4-hydroxypiperidino)-1-propanol

5        NaBH<sub>4</sub> (0.25 g, 6.61 mmol) was added all at once to  
a solution of title product of the preceding Example  
(2.88 g, 6.70 mmol) in ethanol (50 ml). The mixture  
was stirred 20 hours at ambient temperature as a  
precipitate formed. The solid was filtered and dried  
10 to yield 0.60 g of present title product; mp 147-148°C;  
NMR includes 4.17 (d, J = 10Hz, 1H); IR (KBr) 3387,  
3024, 2936, 2909, 1611, 1513, 1453, 1239, 1026, 1011,  
695. The filtrate from the above reaction was  
concentrated, the residue partitioned between ethyl  
15 acetate and water and the phases separated. The  
aqueous phase was extracted with ethyl acetate. The  
combined organic phases were washed with water, dried  
(CaSO<sub>4</sub>) and concentrated to give 2.82 g of additional  
title product.

20        EXAMPLE 12

(1S\*,2S\*)-1-(4-Hydroxyphenyl)-2-(4-benzyl-4-hydroxy-  
piperidino)-1-propanol

Title product of the preceding Example (0.49 g,  
1.14 mmol) and tetrahydrofuran (30 ml) was chilled to  
25 -78°C and ammonia gas (30 ml) was condensed into the  
mixture. Sodium (0.082 g, 3.57 mmol) was added in four  
pieces. The reaction, which gradually turned blue, was  
stirred 15 minutes and then quenched with ammonium  
chloride (0.29 g). The reaction was allowed to warm to  
30 ambient temperature, with the ammonia boiling off. The  
reaction was concentrated and the residue was taken up

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in ethyl acetate and washed with water and brine. The organic phase was dried ( $\text{CaSO}_4$ ) and concentrated to give 0.39 g of white solid. Recrystallization from hexane gave 0.19 g of present title product; NMR (DMSO- $d_6$ ) 7.25-7.11 (m, 5H), 7.08 (d,  $J = 8.2\text{Hz}$ , 2H), 6.68 (d,  $J = 8.6\text{Hz}$ , 2H), 4.14 (s, 1H), 4.09 (d,  $J = 9.2\text{Hz}$ , 1H), 3.33 (s, 2H), 3.30 (s, 1H), 2.74 (m, 1H--partially under water peak from the NMR solvent), 2.60-2.35 (m, 4H--partially under NMR solvent peak), 1.70-1.44 (m, 4H), 0.63 (d,  $J = 6.7\text{Hz}$ , 3H). Deuterium oxide washed out the singlets at 4.14 and 3.30 ppm.

This product was recrystallized from ethyl acetate to give purified title product; mp  $213-214^\circ\text{C}$ ; IR (KBr) 3263, 3023, 2940, 2917, 1615, 1517, 1453, 1273, 1221, 1186, 1020, 1011, 831, 687. Anal. C 73.73, H 8.03, N 4.01, calcd. C 73.87, H 7.97, N 4.10.

#### EXAMPLE 13

1-(4-(tert-Butyldimethylsilyloxy)phenyl)-2-(3-phenylthio-8-azabicyclo[3.2.1]oct-8-yl)-1-propanone

Following the procedure of Example 1, this product was prepared from 4-tert-butyldimethylsilyloxy- $\alpha$ -bromopropiophenone (1.25 g, 3.65 mmol), 3-phenylthio-8-azabicyclo[3.2.1.]octane (0.8 g, 3.65 mmol), and triethylamine (0.51 ml, 3.65 mmol) in ethanol (30 ml) with an overnight reflux. The product was flash chromatographed on silica gel (10% ethyl acetate/hexane elution); 0.889 g (51%); NMR 8.13 (d,  $J = 9\text{Hz}$ , 2H), 7.38 (m, 2H), 7.30-7.15 (m, 3H), 6.83 (d,  $J = 9\text{Hz}$ , 2H), 3.93 (q,  $J = 7\text{Hz}$ , 1H), 3.42-3.28 (m, 3H), 2.05-1.56 (m, 9H), 1.32 (d,  $J = 7\text{Hz}$ , 3H), 0.99 (s, 9H), 0.25 (s, 6H); IR 2940, 2840, 1600, 1390-1290 (br), 910.

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EXAMPLE 14

Mixture of (1R\*,2S\*)- and (1S\*,2S\*)-1-(4-(tert-Butyl-dimethylsilyloxy)phenyl)-2-(3-phenylthio-8-azabicyclo-  
[3.2.1]oct-8-yl)-1-propanol

5

This product was prepared as in Example 2 with overnight stirring at ambient temperature from the product of the preceding Example (0.85 g, 1.77 mmol) and LiAlH<sub>4</sub> (0.153 g, 4.0 mmol) in tetrahydrofuran (24 ml). The product was isolated as a yellow oil (0.78 g, 91%) as a mixture of racemic title products.

10

EXAMPLE 15

(1S\*,2S\*)- and (1R\*,2S\*)-1-(4-Hydroxyphenyl)-2-  
(3-phenylthio-8-azabicyclo[3.2.1]oct-8-yl)-1-propanol

15

Title product of the preceding Example (0.78 g, 1.6 mmol) was desilylated according to the procedure of Example 3 with tetrabutylammonium fluoride (1.6 ml, 1.6 mmol; 1M in tetrahydrofuran) in a 5 minute reaction. The resulting mixture of racemates were separated by silica gel flash chromatography (50% ethyl acetate/hexane elution). (1S\*,2S\*)-Title product eluted first; 0.133 g; NMR (DMSO d<sub>6</sub>) 7.40-7.21 (m, 5H), 7.06 (d, J = 8.5Hz, 2H), 6.63 (d, J = 8.0 Hz, 2H), 4.35 (d, J = 5.0Hz, 1H), 3.54-3.40 (m, 2H), 3.35-3.29 (m, 2H), 2.70-2.62 (br t, 1H), 2.50 (m, 1H), 1.80-1.54 (m, 6H), 0.63 (d, J = 6.5Hz, 3H).

20

25

Continued elution gave (1R\*,2S\*)-title product: 0.102 g; NMR 7.45-7.40 (m, 2H), 7.32-7.22 (m, 3H), 7.15 (d, 2H), 6.76 (d, 2H), 4.80 (d, 1H), 3.60-3.52 (m, 2H), 3.51-3.38 (m, 1H), 2.80-2.72 (m, 1H), 2.00-1.55 (m, 8H), 0.68 (d, 3H). This product (80 mg) was converted to its HCl salt by dissolving in 15ml of ether, bubbling in dry HCl for 2 minutes and triturating the resulting oily solid with ether to yield 30 mg as a white solid.

30

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EXAMPLE 16

2-(4-Benzyl-4-hydroxypiperidino)-1-(4-(triisopropylsilyloxy)phenyl)-1-propanone

5 This product was prepared according to the procedures of Example 1 from 4-hydroxy-4-benzylpiperidine (2.72 g, 14.22 mmol), 4-triisopropylsilyloxy-alpha-bromopropiophenone (5.48 g, 14.22 mmol), and triethylamine (2.0 ml, 14.35 mmol) in ethanol (50 ml) with a reflux time of 17 hours to give 4.92 g (70%) of present, chromatographed title product as an orange oil; NMR 8.01 (d, J = 8.8Hz, 2H), 7.31-7.22 (m, 3H), 7.18-7.15 (m, 2H), 6.87 (d, J=8.8Hz, 2H), 4.03 (q, J = 6.7Hz, 1H), 2.72 (s, 2H), 2.68-2.57 (m, 3H), 2.45 (dt, 1H), 1.78-1.42 (m, 4H), 1.40-1.25 (m, 7H), 1.10 (d, J = 7Hz, 18H).

EXAMPLE 17

(1S\*,2S\*)- and (1R\*,2S\*)-2-(4-Benzyl-4-hydroxypiperidino)-1-(4-(triisopropylsilyloxy)phenyl)-1-propanol

20 Title product of the preceding Example (4.92 g, 9.33 mmol) was dissolved in ethanol (100 ml) and NaBH<sub>4</sub> (0.38 g, 10 mmol) was added all at once. After stirring overnight at ambient temperature, present (1S\*,2S\*)-title product was recovered by filtration, 2.11 g; NMR 7.46-7.17 (m, 7H), 6.84 (d, J = 7Hz, 2H), 4.18 (d, J = 11Hz, 1H), 2.86 (br t, 1H), 2.77 (s, 2H), 2.70-2.42 (m, 4H), 1.89-1.55 (m, 6H), 1.30-1.13 (m, 3H), 1.10 (d, J = 8.6 Hz, 18H), 0.75 (d, J = 6Hz, 3H).

30 The filtrate was concentrated and the residue dissolved in ethyl acetate, extracted with water (2x) and brine, dried (CaSO<sub>4</sub>), concentrated to 2.33 g of a

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light yellow solid, and flash chromatographed on silica gel (2 x 6 inches, ethyl acetate/hexane gradient elution) to give first 1.4 g more of (1S\*,2S\*)-product, followed by 0.46 g of (1R\*,2S\*)-product; NMR 7.33-7.11 (m, 7H), 6.82 (d, J = 8.6Hz, 2H), 4.77 (d, J = 4Hz, 1H), 2.80-2.39 (m, 5H), 1.88-1.43 (m, 6H), 1.31-1.13 (m, 8H), 1.08 (d, J = 6.7Hz, 18H), 0.84 (d, J = 6.9Hz, 3H).

#### EXAMPLE 18

(1R\*,2S\*)-2-(4-Benzyl-4-hydroxypiperidino)-1-(4-hydroxyphenyl)-1-propanol

By the method of Example 3, using ethyl acetate/hexane gradient elution in chromatography, (1R\*,2S\*)-title product of the preceding Example (0.46 g, 0.92 mmol) was converted to 0.24 g (74%) of present title product as a monohydrate; mp 173-174°C; NMR (DMSO d<sub>6</sub> with D<sub>2</sub>O added) 7.21-7.12 (m, 5H), 7.04 (d, J = 7.6Hz, 2H), 6.64 (d, J = 8.6Hz, 2H), 4.64 (d, J = 8.6Hz, 1H), 2.59 (s, 2H), 2.59-2.49 (m, 5H--partially under NMR solvent) 1.50-1.31 (m, 4H), 0.82 (d, J = 7Hz, 3H). Anal. C 70.26, H 7.96, N 3.85; calcd. for monohydrate, C 70.17, H 8.13, N 3.90.

#### EXAMPLE 19

2-(4-Benzyl-4-hydroxypiperidino)-1-(4-fluoro-phenyl)-1-propanone

Title product, prepared as in Example 10 in 80% yield, was recrystallized from ether, mp 119.5-120°C; Anal. C 73.41, H 7.08, N 4.03, calcd. C 73.87, H 7.09, N 4.10.



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EXAMPLE 20

(1S\*,2S\*)- and (1R\*,2S\*)-2-(4-Benzyl-4-hydroxypiperi-  
dino)-1-(4-fluorophenyl)-1-propanol

5 Title products, prepared as in Example 17, were  
separated by flash chromatography on silica gel (ethyl  
acetate-hexane then methanol-ethyl acetate gradient).  
The 1S\*,2S\* product eluted first in 84% yield as a  
solid which was recrystallized from ethanol/ether, mp  
153.5-154.5°C. Anal. C 73.53, H 7.67, N 4.08, calcd. C  
10 73.44, H 7.63, N 4.08.

The 1R\*,2S\* product, eluted second in 15% yield,  
was recrystallized from ethanol/ether, mp 145-146°C;  
Anal. C 73.18, H 7.59, N 4.06, calcd. C 73.44, H 7.63,  
15 N 4.08.

EXAMPLE 21

2-(3-Phenylmethylene-8-azabicyclo[3.2.1]oct-8-yl)-1-  
4-benzyloxyphenyl)-1-propanone

20 Title product, prepared following the procedure of  
Example 1 from 4-benzyloxy-alpha-bromopropiophenone,  
was obtained in 40-60% yield after silica gel flash  
chromatography; NMR 8.34 (d, 2H), 7.56-7.45 (m, 7H),  
7.20 (d, 3H), 7.03 (d, 2H), 6.36 (s, 1H), 5.14 (s, 2H),  
4.13 (q, 1H), 3.56-3.30 (m, 2H), 2.81 (t, 1H),  
25 2.70-2.40 (m, 2H), 2.10-1.76 (m, 3H), 1.66 (m, 1H),  
1.45 (d, 3H).

EXAMPLE 22

(1S\*,2S\*)-2-(3-Phenylmethylene-8-azabicyclo[3.2.1]oct-  
8-yl)-1-(4-benzyloxyphenyl)-1-propanol

30 Title product, prepared following the procedure of  
Example 3 with a 1.25 hour reaction time, was obtained  
in pure form by flash chromatography on silica gel, mp  
145-148°C; Anal. C 81.69, H 7.46, N 3.02, calcd. C  
81.97, H 7.57, N 3.19.

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EXAMPLE 23

(1S\*,2S\*)-2-(3-Benzyl-8-azabicyclo[3.2.1]oct-8-yl)-1-(4-hydroxyphenyl)-1-propanol

5 Title product of the preceding Example (0.23 g, 0.523 mmol) was dissolved in tetrahydrofuran (20 ml) and chilled to -78°C. Ammonia (30 ml) was condensed into the solution. Sodium (0.06 g, 2.6 mmol) was added in three portions and a blue solution gradually formed. After 10 minutes the reaction was quenched with excess ammonium chloride and the mixture was allowed to warm to ambient temperature with evaporation of the ammonia. The residual mixture was concentrated, and the residue extracted with ethyl acetate. Filtration and concentration left 0.24 g of an oily solid which was flash chromatographed on silica gel (6 x 1 inch, ethyl acetate/hexane gradient elution followed by methanol flushing). This gave first recovered starting material followed by product (0.071 g). The product was further purified by recrystallization (ethyl acetate/hexane). A portion was spilled during this process but 0.005 g of white solid product was obtained as a 1:3 mixture of epimers of the benzyl group; NMR 7.30-7.10 (m, 7H), 6.72 (J = 8.5Hz) and 6.71 (J = 8.6Hz) (pair of overlapping d, total 2H), 4.11 (d, J = 8.6Hz, 1H), 3.45 (s, 1H), 3.31 and 3.24 (pair of s, 1H), 2.73 (J = 7.3Hz) and 2.48 (J = 7.2Hz) (pair of d, 2H), 2.61 (quintet, J = 7.6Hz, 1H), 2.11 (m, 1H), 1.86-1.17 (m, 10H), 0.81 (d, J = 6.7Hz, 3H). HRMS 352.2276, calcd. for MH+ 352.2278.

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EXAMPLE 242-(4-Benzyl-4-hydroxypiperidino)-1-(4-chlorophenyl)-1-propanone

5 Title product, prepared from 4-chloro-alpha-bromo-propio-  
phenone, following the procedure of Example 10 in  
72% yield, was purified by flash chromatography on  
silica gel and recrystallized from ether, mp  
135.5-136°C; Anal. C 70.11, H 6.70, N 3.85, calcd. C  
10 70.48, H 6.76, N 3.91.

EXAMPLE 25(1S\*,2S\*)- and (1R\*,2S\*)-2-(4-Benzyl-4-hydroxypiperi-  
dino)-1-(4-chlorophenyl)-1-propanol

15 Title products, prepared following the procedure  
of Example 17, were separated by the same chromato-  
graphic procedure. The 1S\*,2S\* product was obtained in  
70% yield, mp 159.5-160.5°C (ethanol/ether); Anal. C  
70.13, H 7.50, N 3.91, calcd. C 70.08, H 7.28, N 3.89.

The 1R\*,2S\* product was obtained in 7% yield, mp  
20 150.5-151.5°C (ethanol/ether); Anal. C 69.62, H 7.38, N  
3.92, calcd. C 70.08, H 7.28, N 3.89.

EXAMPLE 262-(4-Benzyl-4-hydroxypiperidino)-1-  
(4-chlorophenyl)-1-ethanone

25 Title product was prepared following the procedure  
of Example 10 from 4-chloro-alpha-bromoacetophenone in  
76% yield; NMR 7.93 (d, J = 8.5Hz, 2H), 7.39 (d, J =  
8.6Hz, 2H), 7.31-7.16 (m, 5H), 3.74 (s, 2H), 2.74 (s,  
2H), 2.73-2.71 (m, 2H), 2.43 (dt, J = 11.5, 2.4Hz, 2H),  
30 1.80 (dt, J = 12.7, 4.3Hz, 2H), 1.50 (br d, J = 13.8Hz,  
2H).

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EXAMPLE 272-(4-Benzyl-4-hydroxypiperidino)-1-  
(4-chlorophenyl)ethanol

5 Title product, prepared from 4-chloro-alpha-bromo-  
acetophenone following the procedure of Example 17 in  
83% yield, was recrystallized from ethanol/ether, mp  
151-152°C; NMR 7.34-7.18 (m, 9H), 4.67 (dd, J = 10.5,  
3.5 Hz, 1H), 4.18 (br s, 1H), 2.89-2.86 (m, 1H), 2.76  
10 (s, 1H), 2.68-2.47 (m, 3H), 2.41-2.31 (m, 2H), 1.73  
(dq, J = 13.3, 4.4Hz, 2H), 1.58-1.50 (m, 2H), 1.24 (s,  
1H).

EXAMPLE 282-(4-Benzyl-4-hydroxypiperidino)-1-  
(4-fluorophenyl)-1-ethanone

15 Title product was prepared following the procedure  
of Example 10 in 59% yield from 4-fluoro-alpha-bromo-  
acetophenone; NMR 8.05-7.99 (m, 2H), 7.33-7.04 (m, 7H),  
3.76 (s, 2H), 2.83-2.71 (m, 4H), 2.43 (dt, J = 11.5,  
2.1Hz, 2H), 1.82 (dt, J = 12.7, 4.3Hz, 3H), 1.51 (br d,  
20 J = 11.5Hz, 2H).

EXAMPLE 292-(4-Benzyl-4-hydroxypiperidino)-1-  
(4-fluorophenyl)-1-ethanol

25 Title product, prepared following the procedure of  
Example 17 in 85% yield, was recrystallized from  
ethanol/ether, mp 144.5-146°C; NMR 7.35-7.25 (m, 5H),  
7.19 (d, J = 6.4Hz, 2H), 7.01 (t, J = 8.7Hz, 2H), 4.67  
(dd, J = 10.5, 3.5Hz, 1H), 4.18 (br s, 1H), 2.88 (br d,  
J = 11.2Hz, 1H), 2.76 (s, 2H), 2.68-2.31 (m, 5H),  
30 1.81-1.66 (m, 2H), 1.58-1.50 (m, 2H), 1.28 (s, 1H).

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EXAMPLE 30

Endo-1-(4-(Triisopropylsilyloxy)phenyl)-  
2-(3'-phenylspiro[8-azabicyclo[3.2.1]octane-  
3,2'-oxirane]-8-yl)-1-propanone

5

Title product of Preparation 13 below (0.72 g,  
3.34 mmol), title product of Preparation 10 below  
(1.29 g, 3.35 mmol), and potassium carbonate (0.93 g,  
6.7 mmol) were combined in tetrahydrofuran (80 ml),  
refluxed for 30 hours, cooled and filtered through  
diatomaceous earth. The filtrate was concentrated and  
chromatographed on silica gel (ethyl acetate/hexane  
gradient elution) to give 0.77 g (44%) of title product  
as a mixture of diastereomers. The epoxide protons  
were observed at delta 3.65 and 3.60 ppm in the NMR  
spectrum.

10

15

The corresponding exo isomer was prepared in like  
manner from the other isomer of Preparation 13 in 37%  
yield. The epoxide protons in the mixture of  
diasteromeric products were observed at 3.80 and 3.86  
ppm in the NMR spectrum.

20

EXAMPLE 31

Endo- and exo-(1S\*,2S\*) and (1R\*,2S\*)-1-(4-(Triiso-  
propylsilyloxy)phenyl)-2-(3'-phenylspiro[8-azabicyclo-  
[3.2.1]octane-3,2'-oxirane]-8-yl)-1-propanol

25

A mixture of present endo title products was  
prepared from endo title product of the preceding  
Example in 82% yield by the procedure of Example 17.  
Flash chromatography gave pure, faster running (1S\*,  
2S\*)-isomer; NMR 7.34-7.23 (m, 5H), 7.17 (d, J = 8.5Hz,  
2H), 6.82 (d, J = 8.5Hz, 2H), 4.02 (d, J = 8Hz, 1H),

30

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3.65 (s, 1H), 3.45 (br s, 1H), 3.28 (br s, 1H), 2.65 (quintet, J = 7.2Hz, 1H), 2.54 (dd, J = 13.8, 3.2Hz, 1H), 2.15 (q, J = 8.6Hz, 2H), 1.93-1.72 (m, 4H), 1.40 (d, J = 13.8Hz, 2H). Slower running (1R\*,2S\*)-isomer, which shows a characteristic NMR signal at 4.81 ppm (br s, 1H) was obtained as a mixture with the (1S\*,2S\*)-isomer.

The corresponding exo isomers were prepared in like manner from the exo-isomer of the preceding Example in 82% yield as a 3:1 mixture of (1S\*,2S\*) and (1R\*,2S\*) isomers. The epoxide protons were seen at 3.86 and 3.82 ppm in the NMR spectrum.

#### EXAMPLE 32

Endo-(1S\*,2S\*)-1-(4-Hydroxyphenyl)-2-(3'-phenylspiro[8-azabicyclo-[3.2.1]octane-3,2'-oxirane]-8-yl)-1-propanol

By the method of Example 3, endo-(1S\*,2S\*)-title product of the preceding Example was converted to present title product in 62% yield; mp 204.5-205°C (chloroform/hexane); NMR 7.32-7.25 (m, 5H), 7.17 (d, J = 8.4Hz, 2H), 6.73 (d, J = 6.6Hz, 2H), 5.25 (br s, 1H), 4.01 (d, J = 8.2Hz, 1H), 3.66 (s, 1H), 3.47 (br s, 1H), 3.31 (br s, 1H), 2.65-2.54 (m, 2H), 2.16 (d, J = 8Hz, 2H), 1.89-1.73 (m, 3H), 1.44 (br d, J = 13.9Hz, 1H), 1.24 (br d, J = 14Hz, 1H), 0.83 (d, J = 6.7Hz, 3H).

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EXAMPLE 33

Endo-(1S\*,2S\*)-2-(3-Benzyl-3-hydroxy-  
8-azabicyclo[3.2.1]oct-8-yl)-1-(4-(triisopropyl-  
silyloxy)phenyl)-1-propanol

5           The endo- (1S\*,2S\*)/(1R\*,2S\*) mixture of Example  
31 (0.19 g, 0.36 mmol) was dissolved in tetrahydrofuran  
(20 ml) and chilled to -78°C. Ammonia (30 ml) was  
condensed into the solution and sodium metal (0.08 g)  
10       was added in small chunks over 1 hour. At this time  
the mixture turned deep blue. The reaction was stirred  
10 minutes longer, then quenched with solid NH<sub>4</sub>Cl. The  
ammonia was allowed to evaporate, the residual mixture  
was partitioned between ethyl acetate and water, and  
15       the aqueous layer was extracted with fresh ethyl  
acetate. The combined organic layers were washed with  
brine, dried over CaSO<sub>4</sub> and concentrated to give 0.18 g  
(95%) of a light yellow oil, which was purified by  
flash chromatography on silica gel (ethyl  
20       acetate/hexane gradient elution) to give 0.1 g of  
colorless oil which was the (1S\*,2S\*)-title product;  
NMR 7.33-7.25 (m, 3H), 7.18 (d, J = 8.3Hz, 4H), 6.84  
(d, J = 8.4Hz, 2H), 4.09 (d, J = 7.5Hz, 1H), 3.42 (br  
s, 1H), 3.13 (br s, 1H), 2.70-2.58 (m, 3H), 2.11-1.91  
25       (m, 4H), 1.73-1.51 (m, 4H), 1.30-1.16 (m, 5H), 1.09 (d,  
J = 6.9Hz, 18H), 0.86 (d, J = 6.7Hz, 3H).

EXAMPLE 34

Endo-(1S\*,2S\*)-2-(3-Benzyl-3-hydroxy-8-azabicyclo-  
[3.2.1]oct-8-yl)-1-(4-hydroxyphenyl)-1-propanol

30       By the procedure of Example 3, title product of  
the preceding Example was converted to present title  
product in 38% yield after flash chromatography and

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recrystallization from ethyl acetate/hexane; mp  
162-163°C; <sup>13</sup>C-NMR 156.97, 138.80, 135.86, 131.73,  
129.11, 128.70, 127.07, 115.58, 76.09, 71.74, 64.64,  
62.36, 54.62, 52.97, 45.82, 45.68, 29.28, 28.85, 14.50.

5

By the procedure of the preceding Example, the  
title product of Example 32 is converted to the same  
product.

#### EXAMPLE 35

10

Exo-(1<sub>S</sub>\*,2<sub>S</sub>\*)- and (1<sub>R</sub>\*,2<sub>S</sub>\*)-1-(4-hydroxyphenyl)-  
2-(3'-phenylspiro[8-azabicyclo[3.2.1]octane-3,2'-  
oxirane]-8-yl)-1-propanol

15

By the procedure of Example 3, the exo-(1<sub>S</sub>\*,2<sub>S</sub>\*)/  
(1<sub>R</sub>\*,2<sub>S</sub>\*) mixture of Example 31 was converted to a  
mixture of present title products in 93% yield. The  
(1<sub>S</sub>\*,2<sub>S</sub>\*) isomer was separated by flash chromatography  
and recrystallized from ether/hexane, mp 115-117°C.  
The (1<sub>R</sub>\*,1<sub>S</sub>\*) isomer, obtained as a minor component  
(about 25%) in later fractions of the chromatography,  
was also recrystallized from ether/hexane, mp  
107-110°C.

20

#### EXAMPLE 36

1-(4-(Triisopropylsilyloxy)phenyl)-2-(4-hydroxy-4-  
phenylpiperidino)-1-propanone

25

By the procedure of Example 1, 4-hydroxy-4-phenyl-  
piperidine was converted to present title product in  
37% yield as a clear oil; NMR 8.03 (d, J = 8.5Hz, 2H),  
7.47 (d, J = 8Hz, 2H), 7.33 (t, J = 7.5Hz, 2H),  
7.26-7.24 (m, 1H), 6.89 (d, J = 8.5Hz, 2H), 4.08 (q, J  
= 7.5Hz, 1H), 2.90-2.60 (m, 2H), 2.25-2.10 (m, 2H),  
1.85-1.75 (m, 2H), 1.65-1.55 (m, 2H), 1.32-1.22 (m,  
6H), 1.10 (d, J = 7Hz, 18H).

30



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EXAMPLE 37

(1S\*,2S\*)-1-(4-(Triisopropylsilyloxy)phenyl)-2-  
(4-hydroxy-4-phenylpiperidino)-1-propanol

5 By the procedure of Example 17, title product of  
the preceding Example was converted to present title  
product in 87% yield; mp 148-151°C; NMR 7.52 (d, J =  
7Hz, 2H), 7.38 (t, J = 7Hz, 2H), 7.30-7.25 (m, 1H),  
7.19 (d, J = 8.5Hz, 2H), 6.84 (d, J = 8.5Hz, 2H), 4.23  
10 (d, J = 9.5Hz, 1H), 3.13-3.02 (m, 1H), 2.80-2.58 (m,  
3H), 2.30-2.08 (m, 2H), 1.90-1.78 (m, 2H), 1.29-1.17  
(m, 3H), 1.09 (d, J = 7Hz, 18H), 0.79 (d, J = 6.5Hz,  
3H).

EXAMPLE 38

15 (1S\*,2S\*)-1-(4-Hydroxyphenyl)-2-(4-hydroxy-4-phenyl-  
piperidino)-1-propanol

Title product, prepared following the procedure of  
Example 3 from title product of the preceding Example  
in 65% yield, was recrystallized from ethanol; mp  
20 202-204°C; Anal. C 71.95, H 8.09, N 4.26, calcd. for  
0.5 C<sub>2</sub>H<sub>5</sub>OH, C 71.97, H 8.05, N 4.00.

EXAMPLES 39-56

Using the methods of the preceding Examples, the  
following additional compounds were prepared,  
25 specifying yield to purified material in the final  
step:

39. 2-(4-Benzyl-4-hydroxypiperidino)-1-(4-  
hydroxyphenyl)ethanol; 42%; mp 98-99°C (from ethanol).

40. (1S\*,2S\*)-2-(4-Benzyl-4-hydroxypiperidino)-  
30 1-(4-methoxyphenyl)-1-propanol; 36%; mp 145.5-146°C  
(from ethanol/ether).

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41. (1S\*,2S\*)-2-(4-Benzyl-4-hydroxypiperidino)-1-(4-hydroxyphenyl)-1-pentanol; 55%; mp 158-159°C (from ethanol/ether).
- 5 42. (1R\*,2S\*)-2-(4-Benzyl-4-hydroxypiperidino)-1-(4-hydroxyphenyl)-1-pentanol; 37%; mp 156-157°C (from ether).
43. (1S\*,2S\*)-2-(4-Benzyl-4-hydroxypiperidino)-1-(4-hydroxyphenyl)-1-butanol; 53%; mp 190-191°C (from ethanol).
- 10 44. (1S\*,2S\*)-2-(4-Benzyl-4-hydroxypiperidino)-1-(4-methoxyphenyl)-1-butanol; 61%; mp 143-144°C (purified by flash chromatography on silica gel using ethyl acetate/hexane gradient elution).
- 15 45. 2-(4-Benzyl-4-hydroxypiperidino)-1-(4-cyanophenyl)ethanol; 52%; mp 142-143°C (from ethanol/ether/hexane).
46. 2-(4-Benzyl-4-hydroxypiperidino)-1-(2-hydroxyphenyl)ethanol; 43%; mp 172-173.5°C (from ethanol).
- 20 47. 2-(4-Benzyl-3-hydroxypiperidino)-1-(3-hydroxyphenyl)ethanol; 76%; mp 198-199°C (from ethanol).
48. 1-(4-Chlorophenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol; 63%; mp 155.5-157°C (from ethanol/ether).
- 25 49. (1S\*,2S\*)-2-(4-(4-chlorophenyl)-4-hydroxypiperidino)-1-(4-hydroxyphenyl)-1-propanol; 58%; mp 204-206°C (from ethyl acetate).
50. 2-(4-Hydroxy-4-phenylpiperidino)-1-(2-thienyl)ethanol; 54%; mp 167-168°C (from ethanol).
- 30

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51. (1S\*,2S\*)-Exo-1-(4-Hydroxyphenyl)-2-(3-(2-thienylthio)-8-azabicyclo[3.2.1]oct-8-yl)-1-propanol; 38%; mp 127.5-129°C (from ethyl acetate/hexane).

5 52. (1R\*,2S\*)-Exo-1-(4-Hydroxyphenyl)-2-(3-(2-thienylthio)-8-azabicyclo[3.2.1]oct-8-yl)-1-propanol; 19%; mp 141-142.5°C (from ethyl acetate).

53. (1S\*,2S\*)-Exo-2-(3-(4-chlorophenylthio)-8-azabicyclo[3.2.1]oct-8-yl)-1-(4-hydroxyphenyl)-1-propanol; 84%; mp 181-182.5°C (from ethyl acetate).

10 54. (1R\*,1S\*)-Exo-2-(3-(4-chlorophenylthio)-8-azabicyclo[3.2.1]oct-8-yl)-1-(4-hydroxyphenyl)-1-propanol; 94%; mp 154-156°C (from ethyl acetate/hexane).

15 55. (1S\*,2S\*)-Exo-1-(4-Hydroxyphenyl)-2-(3-(4-methoxyphenylthio)-8-azabicyclo[3.2.1]oct-8-yl)-1-propanol; 55%; mp 118-119°C (from ethyl acetate/hexane).

20 56. (1R\*,2S\*)-Exo-1-(4-Hydroxyphenyl)-2-(3-(4-methoxyphenylthio)-8-azabicyclo[3.2.1]oct-8-yl)-1-propanol; 37%; mp 72-75°C (flash chromatography on silica gel using ethyl acetate/hexane gradient elution and hexane trituration).

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PREPARATION 18-(2,2,2-Trichloroethoxycarbonyl)-3-phenyl-  
methylene-8-azabicyclo[3.2.1.]octane

5 A solution of benzyltriphenylphosphonium chloride (13.26 g, 34.1 mmol) in tetrahydrofuran (400 ml) was chilled to -78°C and butyl lithium (13.6 ml of 2.5M in hexanes, 34 mmol) was added. This resulted in a heterogeneous orange mixture which was stirred 5 minutes at -78°C and then warmed to 0°C. The solution became nearly homogeneous red and

10 N-2,2,2-trichloroethoxycarbonyltropinone (7.1 g, 23.3 mmol; Montzka et al., Tetrahedron Letters, vol, 14, p. 1325, 1974) was added in tetrahydrofuran (20 ml with a 20 ml rinse). The reaction was refluxed 4 days,

15 cooled, and filtered. Concentration of the filtrate left a viscous brown oil. Flash chromatography on silica gel (3 x 6 inches) using first hexane and then an ethylacetate/hexane gradient gave 7.87 g of white solid product (74%); mp 88-89°C, ir (KBr) 3437, 2958, 1700, 1445, 1425, 1321, 1125, 711. Anal. C 54.89, H 4.82, N 3.77, calcd. C 54.49, H 4.84, N 3.74.

20

PREPARATION 23-Phenylmethylene-8-azabicyclo[3.2.1.]octane

25 A mixture of title product of the preceding Preparation (1.0 g, 2.67 mmol), zinc dust (0.88 g, 13.46 mmol), and acetic acid (50 ml) was stirred overnight. The reaction was then heated at 70°C for 22 hours, then cooled and concentrated. The residue was partitioned

30 between ether/ethyl acetate and saturated NaHCO<sub>3</sub>, and the mixture stirred 30 minutes and then filtered over

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diatomaceous earth. The aqueous phase was separated and further extracted with ethyl acetate (2x). The combined organic layers were washed with water and brine, dried ( $\text{CaSO}_4$ ) and concentrated to leave 0.5 g of light yellow oil. Further purification was effected by taking the oil up in 10% HCl. This acid solution was extracted with ethyl acetate (2x). The acidic layer was neutralized over ice with sodium hydroxide and back extracted into ethyl acetate. This organic layer was dried ( $\text{CaSO}_4$ ) and concentrated to leave 0.24 g (48%) of light yellow oil; NMR 7.24 (m, 2H), 7.13 (d,  $J = 6.6\text{Hz}$ , 3H), 6.28 (s, 1H), 3.52 (br d,  $J = 28.2\text{Hz}$ , 2H), 2.56 (t,  $J = 15.4\text{Hz}$ , 3H), 2.26 (d,  $J = 14.7\text{Hz}$ , 1H), 2.12 (d,  $J = 13.9\text{Hz}$ , 1H), 1.64 (m, 3H), 1.40 (m, 1H).

Alternatively, the product was converted to its HCl salt by treating an acetone solution with HCl gas.

#### PREPARATION 3

##### 4-(tert-Butyldimethylsilyloxy)propiophenone

4-Hydroxypropiophenone (15 g, 100 mmol) and imidazole (17 g, 250 mmol) were dissolved in dimethylformamide (50 ml). tert-Butyldimethylsilyl chloride (19.6 g, 130 mmol) in dimethylformamide (40 ml) was added dropwise at ambient temperature. The mixture was stirred 18 hours, then diluted with water (300 ml) and extracted with ether (4 x 200 ml). The combined ether layers were washed with 1M LiCl and brine, dried ( $\text{CaSO}_4$ ), concentrated to an oily solid, flash chromatographed on silica gel using 1:10 ethylacetate:hexane as eluant to yield 26 g of title product which was further purified by short path

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distillation to yield 23.2 g (88%) of purified title product as a hygroscopic white solid; mp 30-31°C; NMR 7.76 (d, J = Hz, 2H), 6.74 (d, J = Hz, 2H), 2.82 (q, J = Hz, 2H), 1.09 (t, J = Hz, 3H), 0.87 (s, 9H), 0.11 (s, 6H).

#### PREPARATION 4

##### 4-(tert-Butyldimethylsilyloxy)-alpha-bromopropiophenone

4-(tert-Butyldimethylsilyloxy)propiophenone (20 g, 75.8 mmol) was dissolved in acetic acid (300 ml) and bromine (3.9 ml, 75.8 mmol in 30 ml of acetic acid) was added dropwise. The orange color of bromine persisted for about 1 minute and then the reaction rapidly decolorized as the bromine was added. The reaction was stirred 1 hour further, then concentrated and the residue flash chromatographed on silica gel (hexane elution) to give 7.12 g of oily product; NMR 7.92 (d, J = 9Hz, 2H), 6.86 (d, J = 9Hz, 2H), 5.22 (q, J = 6.5 Hz, 1H), 1.85 (d, J = 6.5Hz, 3H), 0.96 (s, 9H), 0.22 (s, 6H). <sup>13</sup>C NMR 76.73, 59.55, 40.47, 38.59, 37.68, 25.42.

#### PREPARATION 5

##### O-Methanesulfonyltropine

Tropine (14.2 g, 100 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (210 ml) and triethylamine (23 ml, 160 mmol) was added. Methanesulfonyl chloride (9.3 ml, 120 mmol) was added rapidly dropwise which caused the methylene chloride solution to reflux gently. The mixture was stirred one hour further; then extracted with cold 0.5 molar sodium hydroxide, water, and brine, dried by filtration through phase separating paper and concentrated to yield 13.8 g (65%) of title product as a yellow solid;

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NMR 4.88 (t, J = 5Hz, 1H), 3.10-3.05 (m, 2H), 2.94 (s, 3H), 2.22 (s, 3H), 2.20-2.10 (m, 2H), 2.02-1.88 (m, 6H).

PREPARATION 6

5

3-Phenylthio-8-methyl-8-azabicyclo[3.2.1]octane

NaH (60% in oil; 2.77 g, 69 mmol) was washed with hexane (3x) and then suspended in tetrahydrofuran (300 ml). Thiophenol (6.5 ml, 63 mmol) in tetrahydrofuran (25 ml) was added dropwise over 5 minutes. The milky white suspension which formed, with hydrogen evolution, was stirred 10 minutes and then O-methanesulfonyl-tropine (13.8 g, 63 mmol in 25 ml of tetrahydrofuran) was added all at once. The mixture was refluxed overnight, cooled and filtered through diatomaceous earth with ether wash. The filtrate was diluted with ethyl acetate and washed with cold 1M NaOH, water, and brine, dried (CaSO<sub>4</sub>) and concentrated to yield 11.48 g (78%) of title product as a yellow solid; NMR 7.50-7.18 (m, 5H), 3.32-3.21 (m, 1H), 3.15-3.09 (m, 2H), 2.25 (s, 3H), 2.02-1.94 (m, 2H), 1.79-1.72 (m, 4H), 1.60-1.51 (m, 2H); <sup>13</sup>C NMR 134.8, 132.3, 128.8, 126.9, 61.16, 39.21, 38.38, 37.72, 26.42.

20

PREPARATION 7

25

3-Phenylthio-8-(2,2,2-trichloroethoxycarbonyl)-8-azabicyclo[3.2.1]octane

Title product of the preceding Preparation (11.48 g, 49.3 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.75 g, 5.4 mmol) were mixed with benzene (200 ml) and 2,2,2-trichloroethyl chloroformate (7.5 ml, 54.4 mmol) was added rapidly. The reaction was refluxed 2 hours, cooled, filtered,

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and concentrated. The orange oily residue was dissolved in  $\text{CH}_2\text{Cl}_2$ , washed with saturated  $\text{NaHCO}_3$  and then brine, dried ( $\text{CaSO}_4$ ) and concentrated. The residue was purified by flash chromatography on silica gel (hexane and then 5% ethyl acetate/hexane elution) to give first unreacted thiophenol from the previous reaction and then title product as a yellow oil (13 g, 67%); NMR 7.42-7.23 (m, 5H), 4.72 (AB q,  $J = 12\text{Hz}$ , 2H), 4.35-4.30 (m, 4H), 2.73 (heptet,  $J = 6\text{Hz}$ , 1H), 2.05-1.68 M, 6H). The oil was solidified by trituration with hexane; mp 83-84.5°C; Anal. C 48.47, H 4.58, N 3.49, calcd. C 48.68, H 4.60, N 3.55.

#### PREPARATION 8

##### 3-Phenylthio-8-azabicyclo[3.2.1]octane

Title product of the preceding Preparation (13.0 g, 33 mmol) was dissolved in acetic acid (400 ml) and zinc dust (11 g, 168 mmol) was added. The mixture was heated to 100°C overnight, then concentrated and the residue partitioned between  $\text{CH}_2\text{Cl}_2$  and saturated  $\text{NaHCO}_3$ . The resulting emulsion was cleared by filtration through diatomaceous earth. The phases were separated and the organic layer was dried through phase separating filter paper and concentrated to yield 6.1 g (84%) of title product as a yellow oil which solidified on standing; NMR 7.38-7.36 (m, 2H), 7.29-7.20 (m, 3H), 3.52 (s, 2H), 3.36 (heptet,  $J = 6\text{Hz}$ , 1H), 1.94-1.54 (m, 8H);  $^{13}\text{C}$  NMR 134.0, 132.43, 128.83, 127.06, 54.93, 40.81, 39.01, 28.98.

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-46-

PREPARATION 94-(Triisopropylsilyloxy)propiophenone

By the method of Preparation 3, 4-hydroxypropio-  
phenone and triisopropylsilyl chloride were converted  
to present title product as a clear oil in 100% yield;  
NMR 7.87 (d, J = 8.5Hz, 2H), 6.89 (d, J = 8.5Hz, 2H),  
2.94 (q, J = 7Hz, 2H), 1.32-1.15 (m, 3H), 1.20 (t, J =  
7Hz, 3H), 1.09 (d, J = 7Hz, 18H).

PREPARATION 104-(Triisopropylsilyloxy)-alpha-bromopropiophenone

Title product of the preceding Preparation (60.63  
g, 198 mmol) was dissolved in CCl<sub>4</sub> (1100 ml) and a  
solution of bromine (11 ml, 210 mmol in 60 ml CCl<sub>4</sub>)  
added dropwise. After a portion of the bromine  
solution was added without any noticeable decoloration  
after 15 minutes, acetic acid (1.0 ml) was added in two  
portions. The solution decolorized within 20 minutes  
and the addition was completed fairly rapidly. The  
mixture was stirred 15 minutes more; then the volatile  
HBr was partially removed with the aid of a nitrogen  
stream. The reaction was poured onto water (600 ml)  
and the phases were separated. The organic layer was  
washed with water, saturated NaHCO<sub>3</sub>, water, and brine,  
dried (CaSO<sub>4</sub>), and concentrated to leave 76.2 g (100%)  
of present title produced as a clear yellow oil; NMR  
7.94 (d, J = 9Hz, 2H), 6.91 (d, J = 9Hz, 2H), 5.24 (q,  
J = 6.5Hz, 1H), 1.87 (d, J = 6.5Hz, 2H), 1.33-1.17 (m,  
3H), 1.10 (d, J = 7Hz, 18H).

-47-

PREPARATION 114-Fluoro-alpha-bromopropiophenone

5 Title product, prepared as in Preparation 4 in 86% yield after distillation, was recrystallized from ethanol to afford a white crystalline solid; mp 33-34°C. Anal. C 46.67, H 3.38, calcd. C 46.78, H 3.49.

PREPARATION 124-Chloro-alpha-bromopropiophenone

10 The product, prepared following the procedure of Preparation 10 in 98% yield, was recrystallized from ethanol, mp 78-79°C; Anal. C 43.74, H 3.17, calcd. C 43.67, H 3.26.

PREPARATION 13

15 Endo- and Exo-8-(2,2,2-Trichloroethoxycarbonyl)-3' phenylspiro[8-azabicyclo[3.2.1]octane-3,2'-oxirane]

The title product of Preparation 2 (5.0 g, 13.34 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (80 ml) and  
20 m-chloroperbenzoic acid (2.71 g, 13.35 mmol, 85% purity) added. After stirring at ambient temperature overnight, the mixture was extracted with saturated  $\text{NaHCO}_3$ , then with water and brine, dried through phase separating paper, and concentrated to give 5.3 g of a  
25 glassy yellow oil which was chromatographed on silica gel (ethyl acetate/hexane gradient elution). Recovered starting material was eluted first followed by a fast moving endo epoxide product (2.23 g, 42.8%); mp 78-79°C; Anal. C 52.75, H 4.44, N 3.20, calcd. C 52.26, H 4.64, N 3.59; and finally by a slow moving exo  
30 epoxide product (2.32 g, 44.5%); mp 107-108°C; Anal. C 52.34, H 4.40, N 3.54, calcd. as for endo isomer.

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PREPARATION 14

Endo- and exo- 3'-Phenylspiro[8-azabicyclo[3.2.1]-  
octane-3,2'-oxirane]

5       The fast moving endo product of the preceding  
Example (1.55 g, 3.97 mmol) was dissolved in  
tetrahydrofuran (30 ml) and zinc powder (9.3 g, 142  
mmol) and 1 molar monopotassium phosphate (10 ml) were  
added. After stirring overnight, the mixture was  
10       diluted with water (10 ml), the pH adjusted to 10-11  
with NaCO<sub>3</sub> and filtered over diatomaceous earth with  
ethyl acetate and water wash. The aqueous layer in the  
combined filtrate and washes was separated and washed  
with fresh ethyl acetate. The combined organic layers  
15       were washed with brine, dried (CaSO<sub>4</sub>) and stripped to  
yield 0.85 g (100%) of endo-title product as a yellow  
oil. Short path distillation (110-115°C bath  
temperature, 0.5 mm) gave endo title product as a clear  
colorless oil; NMR 7.34-7.23 (m, 5H), 3.63-3.60 (m,  
20       2H), 3.55 (m, 1H), 2.36 (dd, J = 14.1, 3.5Hz, 1H),  
2.17-2.12 (m, 2H), 1.83-1.81 (m, 2H), 1.70-1.61 (m,  
2H), 1.42 (dt, J = 11.9, 2.2Hz, 1H), 1.18 (dt, J =  
14.5, 2.3Hz, 1H). HRMS 215.1301, calcd. 215.1308.

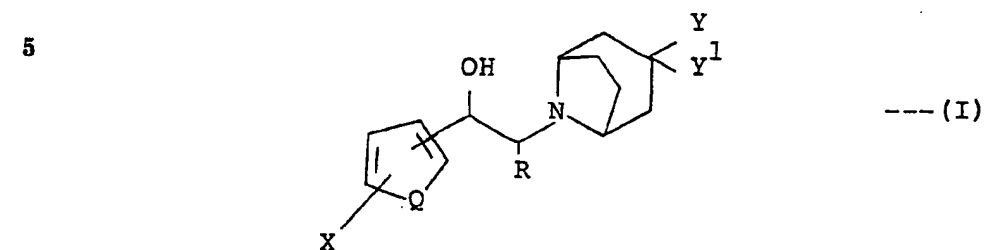
25       By the same method, the slow moving isomer of the  
preceding Preparation was converted to the  
corresponding exo isomer in 96% yield, purified by  
short path distillation (110-125°C bath temperature,  
0.8 mm); mp 114.5-116°C. Anal. C 77.97, H 8.05, N  
6.44, calcd. C 78.10, H 7.96, N 6.51.

30

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CLAIMS

1. A compound of the formula



wherein

R is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl or (C<sub>2</sub>-C<sub>6</sub>)alkynyl;

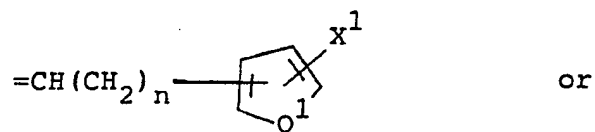
15 Q is S or CH=CH;

X is hydrogen, (C<sub>1</sub>-C<sub>3</sub>)alkyl, halo, OR<sup>1</sup>, OCOR<sup>1</sup>, SR<sup>1</sup>, NHR<sup>1</sup>, NHCOR<sup>1</sup>, CONH<sub>2</sub> or CN;

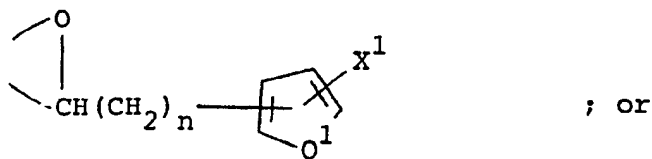
R<sup>1</sup> is hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl;

Y and Y<sup>1</sup> are taken together and are

20



25

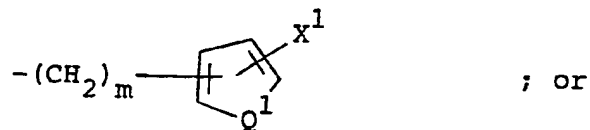


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-50-

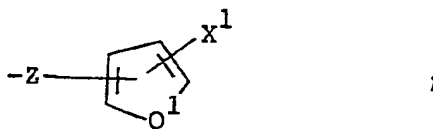
Y and Y<sup>1</sup> are taken separately and  
 Y is hydrogen or OH, and Y<sup>1</sup> is

5



10

Y is hydrogen and Y<sup>1</sup> is



15

n is 0, 1, 2 or 3;

m is 0, 1, 2, 3 or 4;

Q<sup>1</sup> is independently a value of Q as defined above;

20

X<sup>1</sup> is independently a value of X as defined above;

and

Z is O, S, SO or SO<sub>2</sub>; or

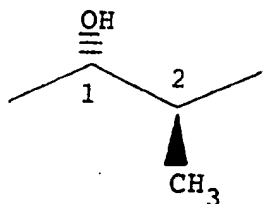
a pharmaceutically acceptable acid addition salt thereof.

25

2. A compound of claim 1 wherein R is methyl having 1S\*,2S\* relative stereochemistry:

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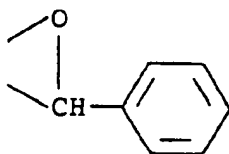
5

3. A compound of claim 1 wherein Q is CH=CH and X is 4-hydroxy.

10 4. A compound of claim 2 wherein Q is CH=CH and X is 4-hydroxy.

5. The compound of claim 4 wherein Y and Y<sup>1</sup> are taken together and are phenylmethylene.

15 6. The compound of claim 4 wherein Y and Y<sup>1</sup> are taken together and are



20

7. A compound of claim 4 wherein Y and Y<sup>1</sup> are taken separately.

8. The compound of claim 7 wherein Y is H and Y<sup>1</sup> is phenylthio.

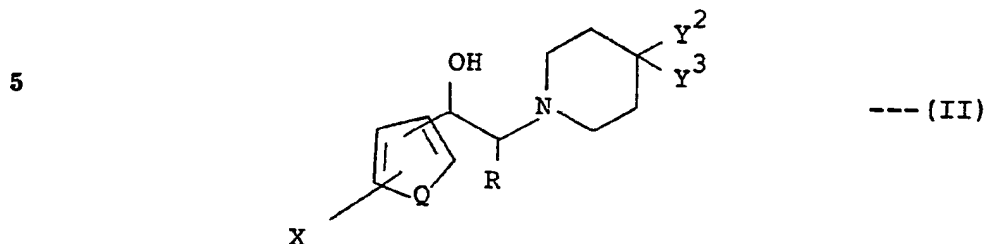
25 9. The compound of claim 7 wherein Y is H and Y<sup>1</sup> is 4-chlorophenylthio.

10. The compound of claim 7 wherein Y is H and Y<sup>1</sup> is 2-thienylthio.

30 11. A compound of claim 7 wherein Y is H or OH and Y<sup>1</sup> is benzyl.

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12. A compound of the formula



10

wherein

R is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl or (C<sub>2</sub>-C<sub>6</sub>)alkynyl;

Q is S or CH=CH;

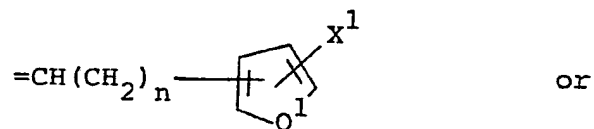
15

X is hydrogen, (C<sub>1</sub>-C<sub>3</sub>)alkyl, halo, OR<sup>1</sup>, OCOR<sup>1</sup>, SR<sup>1</sup>, NHR<sup>1</sup>, NHCOR<sup>1</sup>, CONH<sub>2</sub> or CN;

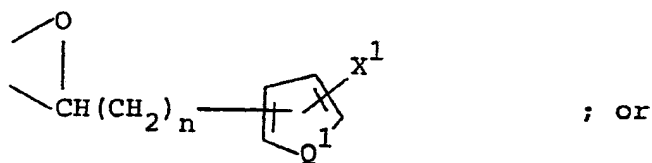
R<sup>1</sup> is hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl;

Y<sup>2</sup> and Y<sup>3</sup> are taken together and are

20



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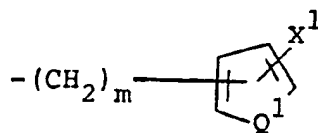


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$Y^2$  and  $Y^3$  are taken separately, and  $Y^2$  is OH and  $Y^3$  is

5



10

$Q^1$  is independently a value of Q as defined above;

$X^1$  is independently a value of X as defined above;

n is 0, 1, 2 or 3; and

m is 0, 1, 2, 3 or 4; or

a pharmaceutically-acceptable acid addition salt thereof.

15

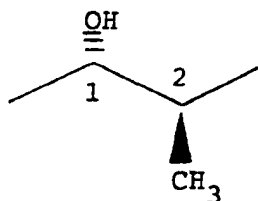
13. A compound of claim 12 wherein Q is CH=CH, X is substituted at the 4-position of the phenyl ring and is hydroxy, fluoro or chloro, and  $Y^2$  and  $Y^3$  are taken separately.

20

14. A compound of claim 13 wherein R is hydrogen, X is 4-fluoro or 4-chloro, and  $Y^3$  is benzyl.

15. A compound of claim 13 wherein R is methyl having 1S\*,2S\* relative stereochemistry:

25



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16. The compound of claim 15 wherein X is 4-hydroxy and Y<sup>3</sup> is benzyl.

17. The compound of claim 15 wherein X is 4-fluoro and Y<sup>3</sup> is benzyl.

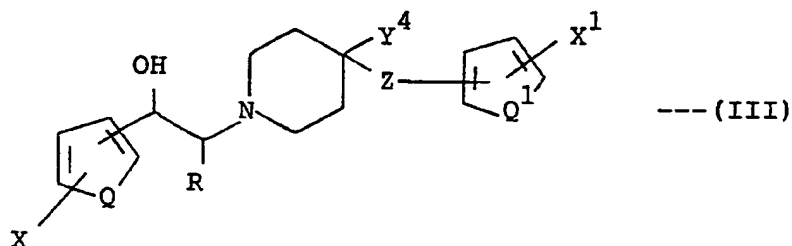
18. The compound of claim 15 wherein X is 4-chloro and Y<sup>3</sup> is benzyl.

19. A compound of claim 15 wherein X is 4-hydroxy and Y<sup>3</sup> is phenyl or 4-chlorophenyl.

20. A compound of claim 12 wherein Q is S forming a 2-thienyl group and X is hydrogen.

21. The compound of claim 20 wherein R is hydrogen, Y<sup>2</sup> and Y<sup>3</sup> are taken separately and Y<sup>3</sup> is phenyl.

22. A compound of the formula



wherein

R is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl or (C<sub>2</sub>-C<sub>6</sub>)alkynyl;

Q and Q<sup>1</sup> are each independently S or CH=CH;

X and X<sup>1</sup> are each independently H, (C<sub>1</sub>-C<sub>3</sub>)alkyl, halo, OR<sup>1</sup>, OCOR<sup>1</sup>, SR<sup>1</sup>, NHR<sup>1</sup>, NHCOR<sup>1</sup>, CONH<sub>2</sub> or CN;

R<sup>1</sup> is H or (C<sub>1</sub>-C<sub>3</sub>)alkyl;

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$Y^4$  is H; and

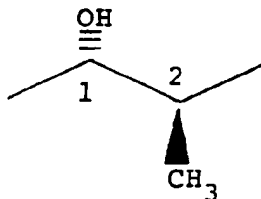
Z is O, S, SO or  $SO_2$ ; or

a pharmaceutically acceptable acid addition salt thereof.

5

23. A compound of claim 22 wherein  $Y^4$  is hydrogen, Q is  $CH=CH$  and R is methyl having  $1S^*, 2S^*$  relative stereochemistry:

10



15

24. The compound of claim 23 wherein X is 4-hydroxy,  $X^1$  is hydrogen and Z is S.

25. The compound of claim 23 wherein X is 4-hydroxy,  $X^1$  is hydrogen and Z is SO.

20

26. The compound of claim 23 wherein X is 4-hydroxy,  $X^1$  is hydrogen and Z is  $SO_2$ .

27. A pharmaceutical composition comprising a neuroprotective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

25

28. A pharmaceutical composition comprising a neuroprotective amount of a compound of claim 12 and a pharmaceutically acceptable carrier.

29. A pharmaceutical composition comprising a neuroprotective amount of a compound of claim 22 and a pharmaceutically acceptable carrier.

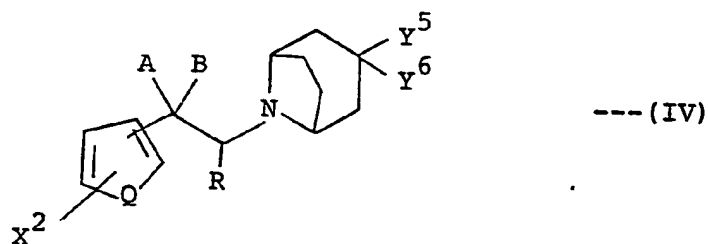
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30. A method of treating stroke or a CNS degenerative disease in man which comprises treatment with a neuroprotective amount of a compound of claim 1.

31. A method of treating stroke or a CNS degenerative disease in man which comprises treatment with a neuroprotective amount of a compound of claim 12.

32. A method of treating stroke or a CNS degenerative disease in man which comprises treatment with a neuroprotective amount of a compound of claim 22.

33. A compound of the formula



wherein

A and B are taken together and are oxygen, or A and B are taken separately and A is hydrogen and B is hydroxy;

R is hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl or (C<sub>2</sub>-C<sub>6</sub>)alkynyl;

Q is S or CH=CH;

$X^2$  is hydrogen,  $(C_1-C_3)$ alkyl, halo,  $OR^1$ ,  $OR^2$ ,  $OCOR^1$ ,  $SR^1$ ,  $SR^2$ ,  $NHR^1$ ,  $NR^1R^3$ ,  $NHCOR^1$ ,  $CONH_2$  or  $CN$ ;

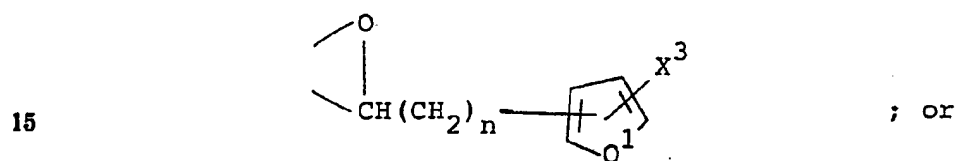
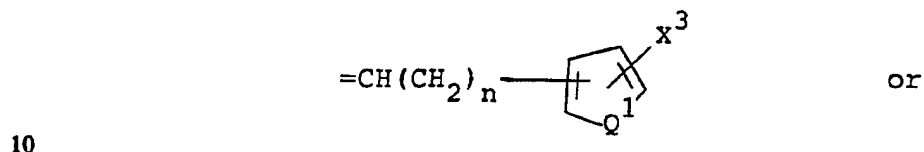
-57-

$R^1$  is hydrogen or  $(C_1-C_3)$ alkyl;

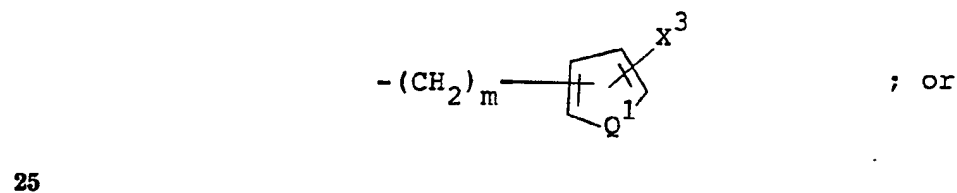
$R^2$  is a conventional hydroxy or mercaptan protecting group;

5  $R^3$  is a conventional amino protecting group;

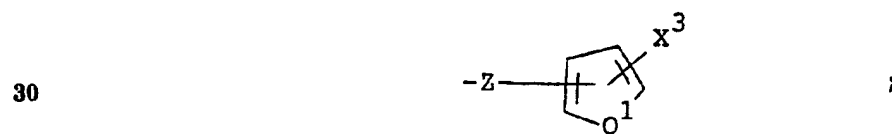
$Y^5$  and  $Y^6$  are taken together and are



20  $Y^5$  and  $Y^6$  are taken separately and  
 $Y^5$  is hydrogen or OH, and  $Y^6$  is



$Y^5$  is hydrogen and  $Y^6$  is



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n is 0, 1, 2 or 3

m is 0, 1, 2, 3 or 4;

$Q^1$  is independently a value of Q as defined above;

5  $X^3$  is independently a value of  $X^2$  as defined above;

Z is O, S, SO or SO<sub>2</sub>;

10 with the proviso that when A and B are taken separately, at least one of  $X^2$  and  $X^3$  is OR<sup>2</sup>, SR<sup>2</sup> or NR<sup>1</sup>R<sup>3</sup>.

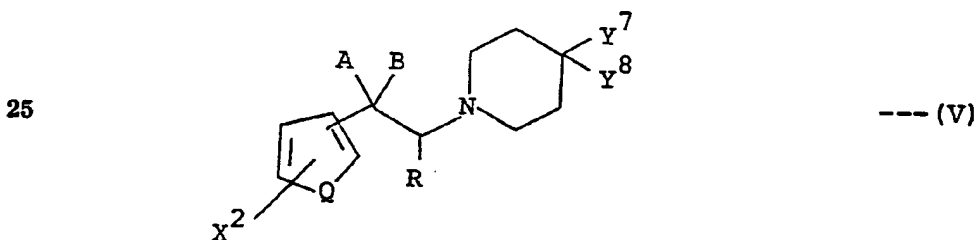
34. A compound of claim 33 wherein A and B are taken separately.

15 35. A compound of claim 34 wherein the conventional hydroxy or mercaptan protecting group is triisopropylsilyl, dimethyl-t-butylsilyl or benzyl.

36. A compound of claim 34 wherein the conventional amino protecting group is benzyloxycarbonyl.

20 37. A compound of claim 33 wherein A and B are taken together.

38. A compound of the formula



30

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wherein

A and B are taken together and are oxygen, or A and B are taken separately and A is hydrogen and B is hydroxy;

R is hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl or (C<sub>2</sub>-C<sub>6</sub>)alkynyl;

Q is S or CH=CH;

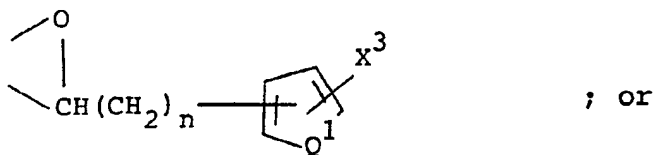
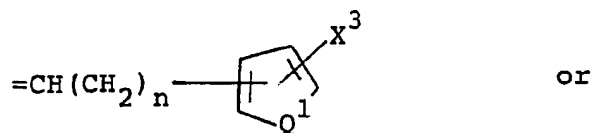
X<sup>2</sup> is hydrogen, (C<sub>1</sub>-C<sub>3</sub>)alkyl, halo, OR<sup>1</sup>, OR<sup>2</sup>, OCOR<sup>1</sup>, SR<sup>1</sup>, SR<sup>2</sup>, NHR<sup>1</sup>, NR<sup>1</sup>R<sup>3</sup>, NHCOR<sup>1</sup>, CONH<sub>2</sub> or CN;

R<sup>1</sup> is hydrogen or (C<sub>2</sub>-C<sub>3</sub>)alkyl;

R<sup>2</sup> is a conventional hydroxy or mercaptan protecting group;

R<sup>3</sup> is a conventional amino protecting group;

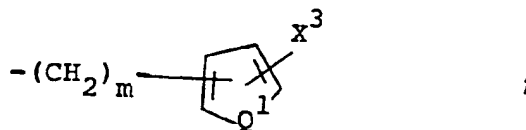
Y<sup>7</sup> and Y<sup>8</sup> are taken together and are



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$Y^7$  and  $Y^8$  are taken separately, and  $Y^7$  is OH and  $Y^8$  is

5



10

$Q^1$  is independently a value of Q as defined above;  
 $X^3$  is independently a value of  $X^2$  as defined

above;

n is 0, 1, 2 or 3;

m is 0, 1, 2, 3 or 4;

15

with the proviso that when A and B are taken separately, at least one of  $X^2$  and  $X^3$  is  $OR^2$ ,  $SR^2$  or  $NR^1R^3$ .

39. A compound of claim 38 wherein A and B are taken separately.

20

40. A compound of claim 39 wherein the conventional hydroxy or mercaptan protecting group is triisopropylsilyl, dimethyl-t-butylsilyl or benzyl.

25

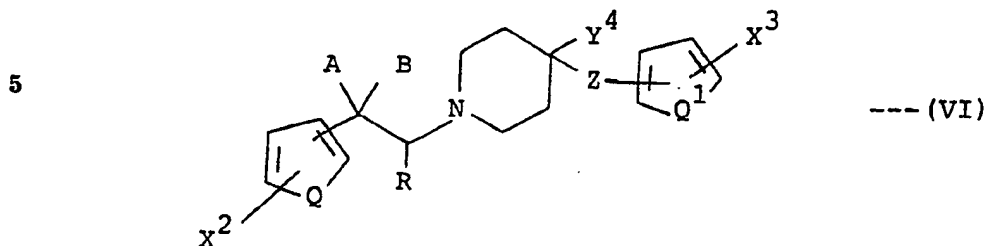
41. A compound of claim 39 wherein the conventional amino protecting group is benzyloxy-carbonyl.

42. A compound of claim 38 wherein A and B are taken together.

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43. A compound of the formula



10

wherein

R is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl or (C<sub>2</sub>-C<sub>6</sub>)alkynyl;

Q and Q<sup>1</sup> are each independently S or CH=CH;

15

X<sup>2</sup> and X<sup>3</sup> are each independently H, (C<sub>1</sub>-C<sub>3</sub>)alkyl, halo, OR<sup>1</sup>, OR<sup>2</sup>, OCOR<sup>1</sup>, SR<sup>1</sup>, SR<sup>2</sup>, NHR<sup>1</sup>, NR<sup>1</sup>R<sup>3</sup>, NHCOR<sup>1</sup>, CONH<sub>2</sub> or CN;

R<sup>1</sup> is H or (C<sub>1</sub>-C<sub>3</sub>)alkyl;

R<sup>2</sup> is a conventional OH or SH protecting group;

20

R<sup>3</sup> is a conventional amino protecting group;

Y<sup>4</sup> is H; and

Z is O, S, SO or SO<sub>2</sub>;

with the proviso that when A and B are taken separately, at least one of X<sup>2</sup> and X<sup>3</sup> is OR<sup>2</sup>, SR<sup>2</sup> or NR<sup>1</sup>R<sup>3</sup>.

25

44. A compound of claim 43 wherein A and B are taken separately.

45. A compound of claim 44 wherein the hydroxy or mercaptan protecting group is triisopropylsilyl, dimethyl-t-butylsilyl or benzyl.

30

46. A compound of claim 44 wherein the amino protecting group is benzyloxycarbonyl.

47. A compound of claim 43 wherein A and B are taken together.



# INTERNATIONAL SEARCH REPORT

International Application No. **PCT/US89/02176**

<b>I. CLASSIFICATION</b> <b>SUBJECT MATTER</b> (if several classification symbols apply, . . . cite all) *	
According to International Patent Classification (IPC) or to both National Classification and IPC <b>IPC(4):</b> A61K 31/46; C07D 451/02; 451/06; 471/20 <b>U.S.Cl.:</b> 514/278,304; 546/18,124,125,129,131	
<b>II. FIELDS SEARCHED</b>	
Minimum Documentation Searched <sup>1</sup>	
Classification System	Classification Symbols
U.S.	514/278,304 546/18,124,125,129,131
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched <sup>2</sup>	
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>3</sup></b>	
Category *	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>
A	US. A, 4,393,069 (LANGBEIN) published 12 July 1983 see entire document.
	Relevant to Claim No. <sup>13</sup> 1-7,11,27 and 30
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents: <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>	
<b>IV. CERTIFICATION</b>	
Date of the Actual Completion of the International Search 10 OCTOBER 1989	Date of Mailing of this International Search Report <div style="text-align: center; font-size: 1.2em; font-weight: bold;">23 OCT 1989</div>
International Searching Authority ISA/US	Signature of Authorized Officer BERNARD DENTZ

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE 1

1. ☐ Claim numbers . because they relate to subject matter <sup>12</sup> not required to be searched by this Authority, namely:

- VI.
- ☒
- OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING:

I. Claims 1-7, 11, 27 and 30 in which Y<sup>1</sup> has a bond or a carbon chain attached to the Q<sup>1</sup> containing ring or where Y and Y<sup>1</sup> form an epoxide containing group. (See Continuation sheet D).

- Remark on Protest**

- ☐ The additional search fees were accompanied by applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

II. Claims 1-4, 8-10, 27 and 30 wherein Y<sup>1</sup> has a hetero atom attached to the Q<sup>1</sup> containing ring.

III. Claims 12-21, 28 and 31.

IV. Claims 22-26, 29 and 32.

V. Claims 33-37 drawn to intermediates for the Group I compounds.

VI. Claims 33-37 drawn to intermediates for the Group II compounds.

VII. Claims 38-42 drawn to intermediates for the Group III compounds.

VIII. Claim 43 drawn to intermediates for the Group IV compounds.

See Form PCT/ISA/206 and its continuation sheet already in the record.